PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/00

A2

(11) International Publication Number: WO 00/27380

(43) International Publication Date: 18 May 2000 (18.05.00)

(21) International Application Number: PCT/US99/26206

(22) International Filing Date: 5 November 1999 (05.11.99)

(30) Priority Data:

60/107,398	6 November 1998 (06.11.98)	US
60/122,977	5 March 1999 (05.03.99)	US
60/122,978	5 March 1999 (05.03.99)	US

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(71) Applicant *(for all designated States except US)*: G.D. SEARLE & CO. [US/US]; Corporate Patent Department, P.O. Box 5110, Chicago, IL 60680–5110 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: PEREZ, Alfonso, T. [US/US]; 1286 Cascade Court, Lake Forest, IL 60045 (US). LACHAPELLE, Richard, J. [US/US]; 1618 Central Avenue, Wilmette, IL 60091 (US). RONIKER, Barbara [US/US]; 1530 Dearborn Parkway, Chicago, IL 60610 (US). ASNER, Debra, J. [US/US]; 9009 Marmora Avenue, Morton Grove, IL 60053 (US). ALEXANDER, John, C. [US/US]; 1100 Pelham Road, Winnetka, IL 60093 (US).

(74) Agents: KEANE, J., Timothy et al.; G.D. Searle & Co., Corporate Patent Department, P.O. Box 5110, Chicago, IL 60680–5110 (US).

(54) Title: COMBINATION THERAPY OF ANGIOTENSIN CONVERTING ENZYME INHIBITOR AND ALDOSTERONE ANTAGONIST FOR REDUCING MORBIDITY AND MORTALITY FROM CARDIOVASCULAR DISEASE

(57) Abstract

Combinations of an ACE inhibitor, an aldosterone antagonist, and a loop diuretic are described for use in treatment of circulatory disorders. Of particular interest are therapies using captopril, enalapril or lisinopril co–administered with spironolactone. This co–therapy would be particularly useful to reduce the death rate or the number of non–fatal hospitalizations or prevent the progression of congestive heart failure in patients with cardiovascular disease.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

COMBINATION THERAPY OF ANGIOTENSIN CONVERTING ENZYME INHIBITOR AND ALDOSTERONE ANTAGONIST FOR REDUCING MORBIDITY AND MORTALITY FROM CARDIOVASCULAR DISEASE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority from U.S. provisional patent application Ser. No.60/107,398 filed on 6 November 1998; U.S. provisional patent application Ser. No. 60/122,977 filed on 5 March 1999; U.S. provisional patent application Ser. No. 60/122,978 filed on 5 March 1999. Each of these priority applications is specifically incorporated herein by reference.

Field of the Invention

Combinations of an angiotensin converting enzyme inhibitor and an aldosterone antagonist are described for use in treatment of circulatory disorders, including cardiovascular diseases such as heart failure, hypertension and congestive heart failure. Of particular interest are therapies using a spirolactone-type aldosterone antagonist compound in combination with an angiotensin converting enzyme inhibitor to reduce the death rate or the number of non-fatal hospitalizations in patients.

Background of the Invention

Myocardial (or cardiac) failure, that is, heart failure ("HF"), whether a consequence of previous myocardial infarction(s), heart disease associated with hypertension, or primary cardiomyopathy, is a major health problem of worldwide proportions. The incidence of symptomatic heart failure has risen steadily over the

past several decades.

In clinical terms, decompensated cardiac failure consists of a constellation of signs and symptoms that arise from congested organs and poorly perfused tissues to form congestive heart failure (CHF) syndrome. Congestion is caused largely by increased venous pressure and by inadequate sodium (Na^+) excretion, relative to dietary Na^+ intake, and is importantly related to circulating levels of aldosterone (ALDO). An abnormal retention of Na^+ occurs via tubular epithelial cells throughout the nephron, including the later portion of the distal tubule and cortical collecting ducts, where ALDO receptor sites are present.

ALDO is the body's most potent mineralocorticoid hormone. As implied by the term mineralocorticoid, this steroid hormone has mineral-regulating activity. It promotes Na^+ reabsorption not only in the kidney, but also from the lower gastrointestinal tract and salivary and sweat glands, each of which represents classic ALDO-responsive tissues. ALDO regulates Na^+ and water resorption at the expense of potassium (K^+) and magnesium (Mg^{2+}) excretion.

ALDO can also provoke responses in non-epithelial cells. Elicited by a chronic elevation in plasma ALDO level that is inappropriate relative to dietary Na^+ intake, these responses can have adverse consequences on the structure of the cardiovascular system. Hence, ALDO can contribute to the progressive nature of myocardial failure for multiple reasons.

Multiple factors regulate ALDO synthesis and metabolism, many of which are operative in the patient with myocardial failure. These include renin as well as

non-renin-dependent factors (such as K^+, ACTH) that promote ALDO synthesis. Hepatic blood flow, by regulating the clearance of circulating ALDO, helps determine ALDO plasma concentration, an important factor in heart failure characterized by reduction in cardiac output and hepatic blood flow.

The renin-angiotensin-aldosterone system ("RAAS") is one of the hormonal mechanisms involved in regulating pressure/volume homeostasis and also in the development of hypertension, a precursor condition implicated in the progression of more serious cardiovascular diseases such as congestive heart failure. Activation of the renin-angiotensin-aldosterone system begins with secretion of the enzyme renin from the juxtaglomerular cells in the kidney. The enzyme renin acts on a naturally-occurring substrate, angiotensinogen, to release a decapeptide, Angiotensin I. This decapeptide is cleaved by angiotensin converting enzyme ("ACE") to provide an octapeptide, Angiotensin II, the primary active species of this system. This octapeptide, angiotensin II, is a potent vasoconstrictor and also produces other physiological effects such as stimulating aldosterone secretion, promoting sodium and fluid retention, inhibiting renin secretion, increasing sympathetic nervous system activity, stimulating vasopressin secretion, causing a positive cardiac inotropic effect and modulating other hormonal systems.

Emphasis has been placed on minimizing hyperaldosteronism as a basis for optimizing patient treatment. This includes the importance of ALDO-receptor antagonism both in patients treated with conventional diuretic programs and in patients treated with angiotensin-converting enzyme (ACE) inhibitors, who

are often constrained to small doses of ACE inhibitor because of orthostatic hypotension. Such patients may demonstrate a recurrence of heart failure symptoms likely related to elevations in plasma ALDO levels.

Many aldosterone blocking drugs and their effects in humans are known. For example, spironolactone is a drug which acts at the mineralocorticoid receptor level by competitively inhibiting aldosterone binding. This steroidal compound has been used for blocking aldosterone-dependent sodium transport in the distal tubule of the kidney in order to reduce edema and to treat essential hypertension and primary hyperaldosteronism [F. Mantero et al, Clin. Sci. Mol. Med., 45 (Suppl 1), 219s-224s (1973)]. Spironolactone is also used commonly in the treatment of other hyperaldosterone-related diseases such as liver cirrhosis and congestive heart failure [F.J. Saunders et al, Aldactone; Spironolactone: A Comprehensive Review, Searle, New York (1978)]. Progressively-increasing doses of spironolactone from 1 mg to 400 mg per day [i.e., 1 mg/day, 5 mg/day, 20 mg/day] were administered to a spironolactone-intolerant patient to treat cirrhosis-related ascites [P.A. Greenberger et al, N. Eng. Reg. Allergy Proc., 7(4), 343-345 (Jul-Aug, 1986)]. It has been recognized that development of myocardial fibrosis is sensitive to circulating levels of both Angiotensin II and aldosterone, and that the aldosterone antagonist spironolactone prevents myocardial fibrosis in animal models, thereby linking aldosterone to excessive collagen deposition [D. Klug et al, Am. J. Cardiol., 71(3), 46A-54A (1993)]. Spironolactone has been shown to prevent fibrosis in animal models irrespective of the development of left ventricular hypertrophy and the presence of hypertension [C.G.

Brilla et al, J. Mol. Cell. Cardiol., 25(5), 563-575 (1993)]. Spironolactone at a dosage ranging from 25 mg to 100 mg daily is used to treat diuretic-induced hypokalemia, when orally-administered potassium supplements or other potassium-sparing regimens are considered inappropriate [Physicians' Desk Reference, 46th Edn., p. 2153, Medical Economics Company Inc., Montvale, N.J. (1992)].

Previous studies have shown that inhibiting ACE inhibits the renin-angiotensin system by substantially complete blockade of the formation of Angiotensin II. Many ACE inhibitors have been used clinically to control hypertension. While ACE inhibitors may effectively control hypertension, side effects are common including chronic cough, skin rash, loss of taste sense, proteinuria and neutropenia.

Moreover, although ACE inhibitors effectively block the formation of Angiotensin II, aldosterone levels are not well controlled in certain patients having cardiovascular diseases. For example, despite continued ACE inhibition in hypertensive patients receiving captopril, there has been observed a gradual return of plasma aldosterone to baseline levels [J. Staessen et al, J. Endocrinol., 91, 457-465 (1981)]. A similar effect has been observed for patients with myocardial infarction receiving zofenopril [C. Borghi et al, J. Clin. Pharmacol., 33, 40-45 (1993)]. This phenomenon has been termed "aldosterone escape".

Combinations of an aldosterone antagonist and an ACE inhibitor have been investigated for treatment of heart failure. It is known that mortality is higher in patients with elevated levels of plasma aldosterone and

that aldosterone levels increase as CHF progresses from RAAS activation. Routine use of a diuretic may further elevate aldosterone levels. ACE inhibitors consistently inhibit angiotensin II production but exert only a mild and transient antialdosterone effect.

Combining an ACE inhibitor and spironolactone has been suggested to provide substantial inhibition of the entire RAAS. For example, a combination of enalapril and a 25 mg daily dose of spironolactone has been administered to ambulatory patients with monitoring of blood pressure [P. Poncelet et al, Am. J. Cardiol., 65(2), 33K-35K (1990)]. In a 90-patient study, a combination of spironolactone at a dose in a range from 50mg/day to 100 mg/day (average 73 mg/day) and captopril was administered and found effective to control refractory CHF without serious incidents of hyperkalemia [U. Dahlstrom et al, Am. J. Cardiol., 71, 29A-33A (21 Jan 1993)]. Spironolactone dosage at 100 mg/day coadministered with an ACE inhibitor was reported to be highly effective in 13 of 16 patients afflicted with congestive heart failure, with a 25 mg/day to 50 mg/day spironolactone maintenance dosage given at trial completion to compensated patients being treated with an ACE inhibitor and loop diuretic [A.A. van Vliet et al, Am. J. Cardiol., 71, 21A-28A (21 Jan 1993)]. Clinical improvements have been reported for patients receiving a co-therapy of spironolactone and the ACE inhibitor enalapril, although this report mentions that controlled trials are needed to determine the lowest effective doses and to identify which patients would benefit most from combined therapy [F. Zannad, Am. J. Cardiol., 71(3), 34A-39A (1993)].

Spironolactone, in combination with ACE inhibitors and loop diuretic therapy, has been shown to be effective in reducing N-terminal pro-atrial natriuretic factor, a marker of heart failure, in patients with that disease [The RALES Investigators, Am. J. Cardiol., 78(8), 902-907 (1996)].

Low dosages of spironolactone (e.g., less than 25 mg per day) for use in treating cardiovascular diseases such as hypertension and heart failure, are described in PCT Application WO 96/24358, published 15 Aug 96.

Combination of an ACE inhibitor and low dosages of spironolactone (less than 25 mg per day) for treating congestive heart failure are described in PCT Application WO 96/24373, published 15 Aug 96.

Use of combinations of ACE inhibitors, low dosages of spironolactone (less than 25 mg/day) and diuretic agents for treating congestive heart failure, are described in PCT Application WO 96/24372, published 15 Aug 96.

Summary of Drawing Figures

Fig. 1A shows a preliminary Kaplan-Meier analysis of mortality among patients with severe heart failure in placebo and spironolactone treated groups. Both groups were co-administered stable doses of an ACE inhibitor and a loop diuretic.

Fig. 1B shows an audited analysis using the Kaplan-Meier method of mortality among patients with severe heart failure in placebo and spironolactone treated

groups. Both groups were co-administered stable doses of an ACE inhibitor and a loop diuretic.

Fig. 2 shows the risk reduction in mortality and 95% confidence interval for patients treated with spironolactone co-therapy, according to various baseline (pre-randomization) variables.

Fig. 3 shows a Kaplan-Meier analysis of combined end-point of non-fatal hospitalization plus total mortality in placebo and spironolactone treated groups. Both groups were co-administered stable doses of an ACE inhibitor and a loop diuretic.

Fig. 4 shows relative risks of death from all causes and according to demographic and clinical characteristics.

Fig. 5 shows the percentage of deaths according to baseline heart failure etiology, subclassified by ejection fraction.

Fig. 6 shows the percentage of deaths according to to baseline heart failure etiology, subclassified by New York Heart Association Class.

Fig. 7 shows relative risk of death from all causes according to baseline characteristics.

Fig. 8 Shows risk reduction by ejection fraction tertiles for spironolactone relative to placebo.

Fig. 9 shows mortality rates according to baseline New York Heart Association Class for spironolactone relative to placebo.

Fig. 10 shows mortality rates according to baseline heart failure etiology for spironolactone relative to placebo.

Description of the Invention

Treatment or prevention of circulatory disorders, including cardiovascular disorders such as heart failure, hypertension and congestive heart failure, is provided by a combination therapy comprising a therapeutically-effective amount of an angiotensin converting enzyme ("ACE") inhibitor along with a therapeutically-effective amount of a spirolactone-type aldosterone antagonist. Preferably, the combination therapy comprises administering therapeutically effective amounts of an ACE inhibitor, an aldosterone antagonist, and a diuretic wherein the diuretic has no substantial aldosterone receptor antagonistic effect.

The combination therapy of the invention would be useful, for example, to reduce the death rate or the number of non-fatal hospitalizations or to prevent or retard, in subjects, the development of congestive heart failure which typically arises from essential hypertension or from heart conditions following myocardial infarct. A diuretic agent may also be used in conjunction with an ACE inhibitor and an aldosterone antagonist.

Alternatively, the combination therapy can comprise administering an angiotensin converting enzyme inhibitor, an aldosterone antagonist and a loop diuretic to the subject, wherein the angiotensin converting enzyme inhibitor, the aldosterone antagonist and the loop diuretic are administered at doses that in combination result in one or more of the following: (1) a statistically significant reduction in the death rate as compared to said combination therapy without the aldosterone antagonist; (2) a statistically significant reduction in the number of non-fatal hospitalizations as compared to said combination therapy without the aldosterone antagonist; (3) a statistically significant

reduction in the death rate or the number of non-fatal hospitalizations as compared to said combination therapy without the aldosterone antagonist; (4) a statistically significant reduction in the rate of deaths resulting from sudden death in subjects afflicted with or susceptible to elevated heart rate variability as compared to said combination therapy without the aldosterone antagonist; (5) a statistically significant reduction in the death rate for deaths resulting from progression of heart failure as compared to said combination therapy without the aldosterone antagonist; (6) a statistically significant reduction in the death rate or the number of non-fatal hospitalizations in subjects having a left ventricular ejection fraction greater than about 26% as compared to said combination therapy without the aldosterone antagonist; (7) a statistically significant reduction in the death rate or the number of non-fatal hospitalizations in subjects having a left ventricular ejection fraction less than about 26% as compared to said combination therapy without the aldosterone antagonist; and/or (8) suppression of clinically significant cough due to elevated pulmonary arterial fibrosis or low levels of pulmonary blood pressure in the subject as compared to said combination therapy.

Still alternatively, the combination therapy may comprise administering a therapeutically-effective amount of an angiotensin converting enzyme inhibitor, a therapeutically-effective amount of an aldosterone antagonist, a therapeutically-effective amount of a loop

diuretic and a therapeutically-effective amount of digoxin to the subject.

Preferably, the subject receiving the combination therapy: (1) is susceptible to sudden death; (2) is classified in New York Heart Association class III or class IV prior to combination therapy; (3) has a left ventricular ejection fraction greater than about 26%; and/or (4) is susceptible to or suffering from clinically significant cough due to elevated pulmonary arterial fibrosis or low levels of pulmonary blood pressure.The phrase "angiotensin converting enzyme inhibitor" ("ACE inhibitor") is intended to embrace an agent or compound, or a combination of two or more agents or compounds, having the ability to block, partially or completely, the rapid enzymatic conversion of the physiologically inactive decapeptide form of angiotensin ("Angiotensin I") to the vasoconstrictive octapeptide form of angiotensin ("Angiotensin II"). Blocking the formation of Angiotensin II can quickly affect the regulation of fluid and electrolyte balance, blood pressure and blood volume, by removing the primary actions of Angiotensin II. Included in these primary actions of Angiotensin II are stimulation of the synthesis and secretion of aldosterone by the adrenal cortex and raising blood pressure by direct constriction of the smooth muscle of the arterioles.

The phrase "aldosterone antagonist" embraces an agent or compound, or a combination of two or more of such agents or compounds, which counteract the effect of aldosterone. Such agents and compounds, such as mespirenone, may antagonize the action of aldosterone through pre-receptor mechanism. Other agents and

compounds, such as spironolactone and eplerenone, fall generally within a class known as aldosterone receptor antagonists and bind to aldosterone receptors such as typically are found in renal tubules, and prevent natural ligand activation of post-receptor events.

The term "spirolactone-type" is intended to characterize a steroidal structure comprising a lactone moiety attached to a steroid nucleus, typically at the steroid "D" ring, through a spiro bond configuration. A subclass of spirolactone-type aldosterone antagonist consists of epoxy-steroidal aldosterone antagonist compounds such as eplerenone. Another subclass of spirolactone-type antagonist consists of non-epoxy-steroidal aldosterone antagonist compounds such as spironolactone.

The phrase "combination therapy" (or "co-therapy"), in defining use of an ACE inhibitor agent, an aldosterone antagonist agent, loop diuretic agent, and/or digoxin is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as by oral ingestion of a single capsule having a fixed ratio of these active agents or ingestion of multiple, separate capsules for each agent. "Combination therapy" will also include simultaneous or sequential administration by intravenous, intramuscular or other parenteral routes into the body, including direct absorption through mucuous membrane tissues, as found in the sinus passages. Sequential administration also includes drug combination where the individual elements may be administered at different times and/or

by different routes but which act in combination to provide a beneficial effect.

The phrase "therapeutically-effective" is intended to qualify the amount of each agent for use in the combination therapy which will achieve the goal of improvement in cardiac sufficiency by reducing or preventing, for example, the progression of congestive heart failure, while avoiding adverse side effects typically associated with each agent.

A preferred combination therapy would consist essentially of two active agents, namely, an ACE inhibitor agent and aldosterone antagonist agent. The agents would be used in combination in a weight ratio range from about 0.5-to-one to about twenty-to-one of the angiotensin converting enzyme agent to the aldosterone antagonist agent. A preferred range of these two agents (ACE inhibitor-to-ALDO antagonist) would be from about one-to-one to about fifteen-to-one, while a more preferred range would be from about one-to-one to about five-to-one, depending ultimately on the selection of the ACE inhibitor and ALDO antagonist. A more preferred combination therapy would consist essentially of three active agents, namely, an ACE inhibitor agent, an aldosterone antagonist agent, and a loop diuretic agent.

Examples of ACE inhibitors which may be used in the combination therapy are shown in the following categories.

A representative group of ACE inhibitors consists of the following compounds: AB-103, ancovenin, benazeprilat, BRL-36378, BW-A575C, CGS-13928C, CL-242817, CV-5975, Equaten, EU-4865, EU-4867, EU-5476,

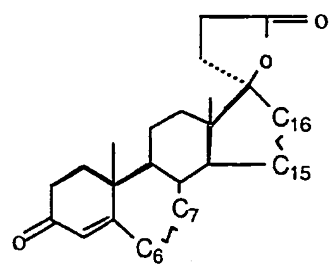
foroxymithine, FPL 66564, FR-900456, Hoe-065, I5B2, indolapril, ketomethylureas, KRI-1177, KRI-1230, L-681176, libenzapril, MCD, MDL-27088, MDL-27467A, moveltipril, MS-41, nicotianamine, pentopril, phenacein, pivopril, rentiapril, RG-5975, RG-6134, RG-6207, RGH-0399, ROO-911, RS-10085-197, RS-2039, RS 5139, RS 86127, RU-44403, S-8308, SA-291, spiraprilat, SQ-26900, SQ-28084, SQ-28370, SQ-28940, SQ-31440, Synecor, utibapril, WF-10129, Wy-44221, Wy-44655, Y-23785, Yissum P-0154, zabicipril, Asahi Brewery AB-47, alatriopril, BMS 182657, Asahi Chemical C-111, Asahi Chemical C-112, Dainippon DU-1777, mixanpril, Prentyl, zofenoprilat, 1-(-(1-carboxy-6-(4-piperidinyl)hexyl)amino)-1-oxopropyl octahydro-1H-indole-2-carboxylic acid, Bioproject BP1.137, Chiesi CHF 1514, Fisons FPL-66564, idrapril, Marion Merrell Dow MDL-100240, perindoprilat and Servier S-5590, alacepril, benazepril, captopril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, fosinoprilat, imidapril, lisinopril, perindopril, quinapril, ramipril, saralasin acetate, temocapril, trandolapril, ceranapril, moexipril, quinaprilat and spirapril.

A group of ACE inhibitors of high interest consists of the following compounds: alacepril, benazepril, captopril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, fosinoprilat, imidapril, lisinopril, perindopril, quinapril, ramipril, saralasin acetate, temocapril, trandolapril, ceranapril, moexipril, quinaprilat and spirapril.

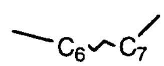
Many of these ACE inhibitors are commercially available, especially those listed in the above group. For example, a highly preferred ACE inhibitor, captopril, is sold by E.R. Squibb & Sons, Inc.,

Princeton, N.J., now part of Bristol-Myers-Squibb, under the trademark "CAPOTEN", in tablet dosage form at doses of 12.5 mg, 50 mg and 100 mg per tablet. Enalapril or Enalapril Maleate, and Lisinopril are two more highly preferred ACE inhibitors sold by Merck & Co, West Point, Pa. Enalapril is sold under the trademark "VASOTEC" in tablet dosage form at doses of 2.5 mg, 5 mg, 10 mg and 20 mg per tablet. Lisinopril is sold under the trademark "PRINIVIL" in tablet dosage form at doses of 5 mg, 10 mg, 20 mg and 40 mg per tablet.

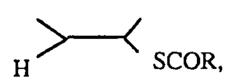
A family of spirolactone-type compounds of interest is defined by Formula I



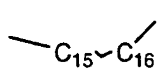
(I)

wherein 

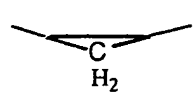
is

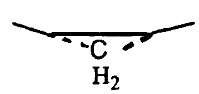
or


wherein R is lower alkyl of up to 5 carbon atoms, and

wherein 

is

 , 

or


.

Lower alkyl residues include branched and unbranched groups, preferably methyl, ethyl and n-propyl.

Specific compounds of interest within Formula I are the following:

7α-Acetylthio-3-oxo-4,15-androstadiene-[17(β-1')-spiro-5']perhydrofuran-2'-one;

3-Oxo-7α-propionylthio-4,15-androstadiene-[17((β-1')-spiro-5']perhydrofuran-2'-one;

6β,7β-Methylene-3-oxo4,15-androstadiene-[17((β-1')-spiro-5']perhydrofuran-2'-one;

15α,16α-Methylene-3-oxo-4,7α-propionylthio-4-androstene[17(β-1')-spiro-5']perhydrofuran-2'-one;

6β,7β,15α,16α-Dimethylene-3-oxo-4-androstene [17(β-1')-spiro-5']perhydrofuran-2'-one;

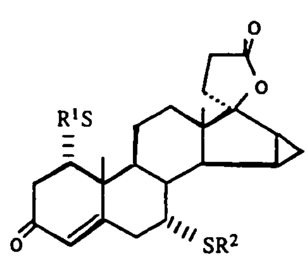
7α-Acetylthio-15β,16β-Methylene-3-oxo-4-androstene-[17(β-1')-spiro-5']perhydrofuran-2'-one;

15β,16β-Methylene-3-oxo-7β-propionylthio-4-androstene-[17(β-1')-spiro-5']perhydrofuran-2'-one; and

6β,7β,15β,16β-Dimethylene-3-oxo-4-androstene-[17(β-1')-spiro-5']perhydrofuran-2'-one.

Methods to make compounds of Formula I are described in U.S. Patent No. 4,129,564 to Wiechart et al issued on 12 December 1978.

A second family of spirolactone-type compounds of interest is defined by Formula II:



(II)

wherein R^1 is C_{1-3}-alkyl or C_{1-3} acyl and R^2 is H or C_{1-3}-alkyl.

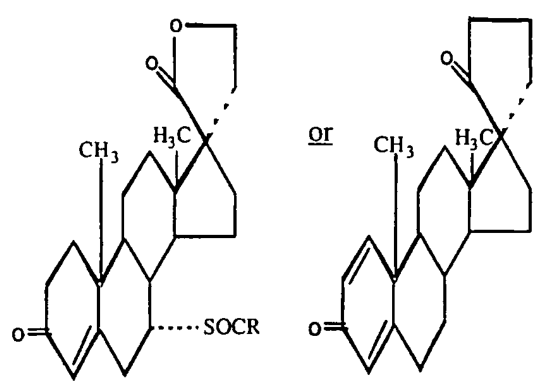
Specific compounds of interest within Formula II are the following:

1α-Acetylthio-15β,16β-methylene-7α-methylthio-3-oxo-17α-pregn-4-ene-21,17-carbolactone; and

15β,16β-Methylene-1α,7α-dimethylthio-3-oxo-17α-pregn-4-ene-21,17-carbolactone.

Methods to make the compounds of Formula II are described in U.S. Patent No. 4,789,668 to Nickisch et al which issued 6 December 1988.

A third family of spirolactone-type compounds of interest is defined by a structure of Formula III:



(III)

wherein R is lower alkyl, with preferred lower alkyl groups being methyl, ethyl, propyl and butyl. Specific compounds of interest include:

3β,21-dihydroxy-17α-pregna-5,15-diene-17-carboxylic acid γ-lactone;

3β,21-dihydroxy-17α-pregna-5,15-diene-17-carboxylic

acid γ-lactone 3-acetate;

3β,21-dihydroxy-17α-pregn-5-ene-17-carboxylic acid γ-lactone;

3β,21-dihydroxy-17α-pregn-5-ene-17-carboxylic acid γ-lactone 3-acetate;

21-hydroxy-3-oxo-17α-pregn-4-ene-17-carboxylic acid γ-lactone;

21-hydroxy-3-oxo-17α-pregna-4,6-diene-17-carboxylic acid γ-lactone;

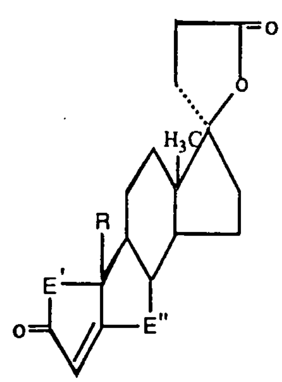
21-hydroxy-3-oxo-17α-pregna-1,4-diene-17-carboxylic acid γ-lactone;

7α-acylthio-21-hydroxy-3-oxo-17α-pregn-4-ene-17-carboxylic acid γ-lactones; and

7α-acetylthio-21-hydroxy-3-oxo-17α-pregn-4-ene-17-carboxylic acid γ-lactone.

Methods to make the compounds of Formula III are described in U.S. Patent No. 3,257,390 to Patchett which issued 21 June 1966.

A fourth family of compounds of interest is represented by Formula IV:

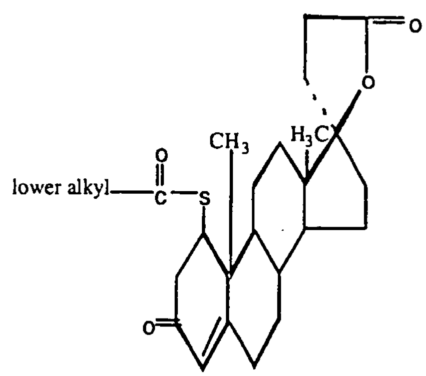


(IV)

wherein E′ is selected from the group consisting of ethylene, vinylene and (lower alkanoyl)thioethylene radicals, E″ is selected from the group consisting of

ethylene, vinylene, (lower alkanoyl)thioethylene and (lower alkanoyl)thiopropylene radicals; R is a methyl radical except when E′ and E″ are ethylene and (lower alkanoyl) thioethylene radicals, respectively, in which case R is selected from the group consisting of hydrogen and methyl radicals; and the selection of E′ and E″ is such that at least one (lower alkanoyl)thio radical is present.

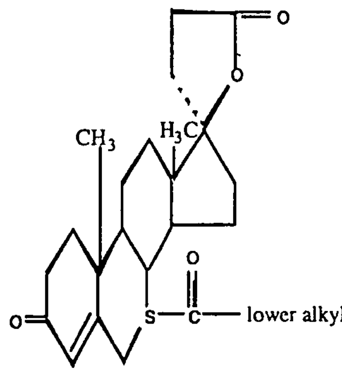
A preferred family of compounds within Formula IV is represented by Formula V:



(V)

A more preferred compound of Formula V is 1-acetylthio-17α-(2-carboxyethyl)-17β-hydroxy-androst-4-en-3-one lactone.

Another preferred family of compounds within Formula IV is represented by Formula VI:



(VI)

More preferred compounds within Formula VI include the following:

7α-acetylthio-17α-(2-carboxyethyl)-17β-hydroxy-androst-4-en-3-one lactone;

7β-acetylthio-17α-(2-carboxyethyl)-17β-hydroxy-androst-4-en-3-one lactone;

1α,7α-diacetylthio-17α-(2-carboxyethyl)-17β-hydroxy-androsta-4,6-dien-3-one lactone;

7α-acetylthio-17α-(2-carboxyethyl)-17β-hydroxy-androsta-1,4-dien-3-one lactone;

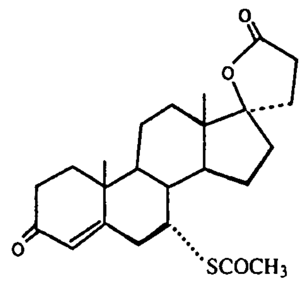
7α-acetylthio-17α-(2-carboxyethyl)-17β-hydroxy-19-norandrost-4-en-3-one lactone; and

7α-acetylthio-17α-(2-carboxyethyl)-17β-hydroxy-6α-methylandrost-4-en-3-one lactone;

In Formula IV-VI, the term "alkyl" is intended to embrace linear and branched alkyl radicals containing one to about eight carbons. The term "(lower alkanoyl)thio" embraces radicals of the formula lower

$$\text{alkyl}-\overset{\overset{\displaystyle O}{\|}}{C}-S\,.$$

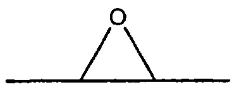
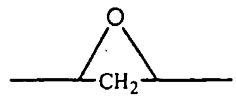
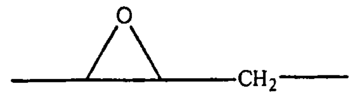
Of particular interest is the compound spironolactone having the following structure and formal name:



"spironolactone": 17-hydroxy-7α-mercapto-3-oxo-17α-pregn-4-ene-21-carboxylic acid γ-lactone acetate

Methods to make compounds of Formula IV-VI are described in U.S. Patent No. 3,013,012 to Cella et al which issued 12 December 1961. Spironolactone is sold by G.D. Searle & Co., Skokie, Illinois, under the trademark "ALDACTONE", in tablet dosage form at doses of 25 mg, 50 mg and 100 mg per tablet.

Another group of aldosterone antagonists of particular interest are epoxy steroidal aldosterone antagonist compounds having a steroidal nucleus substituted with an epoxy-type moiety. The term "epoxy-type" moiety is intended to embrace any moiety characterized in having an oxygen atom as a bridge between two carbon atoms, examples of which include the following moieties:

epoxyethyl 1,3-epoxypropyl 1,2-epoxypropyl

The term "steroidal", as used in the phrase "epoxy-steroidal", denotes a nucleus provided by a cyclopenteno-phenanthrene moiety, having the conventional "A", "B", "C" and "D" rings. The epoxy-type moiety may be attached to the cyclopentenophenanthrene nucleus at any attachable or substitutable positions, that is, fused to one of the rings of the steroidal nucleus or the moiety may be substituted on a ring member of the ring system. The phrase "epoxy-steroidal" is intended to embrace a steroidal nucleus having one or a plurality of epoxy-type moieties attached thereto.

Epoxy-steroidal aldosterone antagonists suitable for use in the present methods include a family of compounds having an epoxy moiety fused to the "C" ring of the steroidal nucleus. Especially preferred are 20-spiroxane compounds characterized by the presence of a 9 α,11α-substituted epoxy moiety. Compounds 1 through 11, below, are illustrative 9α,11α-epoxy-steroidal compounds that may be used in the present methods. These epoxy steroids may be prepared by procedures described in Grob et al., U.S. Patent No. 4,559,332. Additional processes for the preparation of 9,11-epoxy steroidal compounds and their salts are disclosed in Ng et al., WO97/21720 and Ng et al., WO98/25948.

TABLE I: Aldosterone Receptor Antagonist

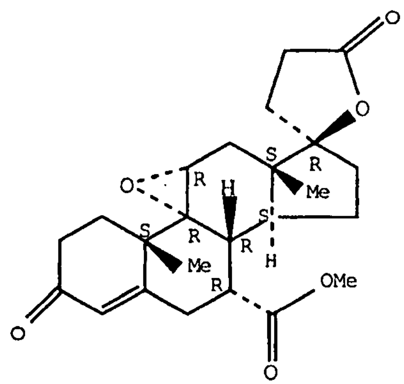
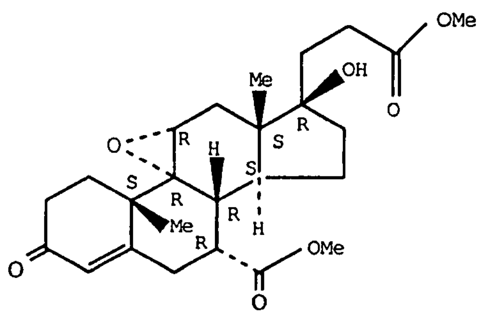
Compound #	Structure	Name
1		Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,γ-lactone, methyl ester, (7α,11.α.,17α)-
2		Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,dimethyl ester,(7α,11α,17α)-

TABLE I: Aldosterone Receptor Antagonist

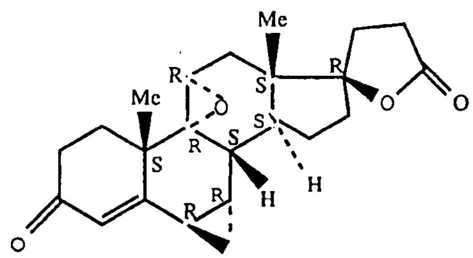
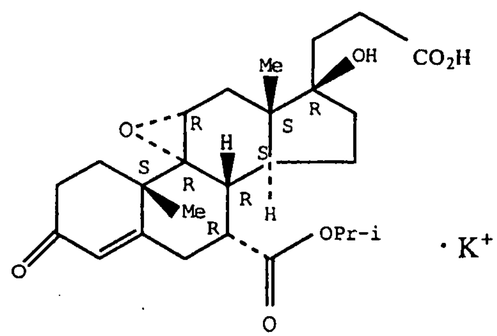
Compound #	Structure	Name
3		3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, γ-lactone, (6β, 7β, 11β, 17β)-
4		Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, 7-(1-methylethyl) ester, monopotassium salt, (7α, 11α, 17α)-

TABLE I: Aldosterone Receptor Antagonist

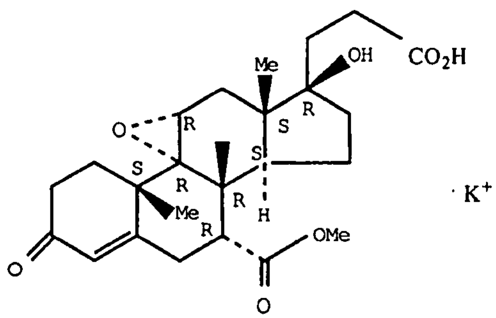
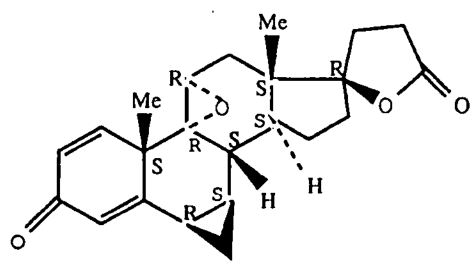
Compound #	Structure	Name
5		Pregn-4-ene-7,21-dicarboxylic acid,9,11-epoxy-17-hydroxy-3-oxo-,7-methylethyl) ester, monopotassium salt,(7α,11α,17α)-
6		3'H-cyclopropa[6,7]pregna-1,4,6-triene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,γ-lactone(6α,7α,11.α)-

TABLE I: Aldosterone Receptor Antagonist

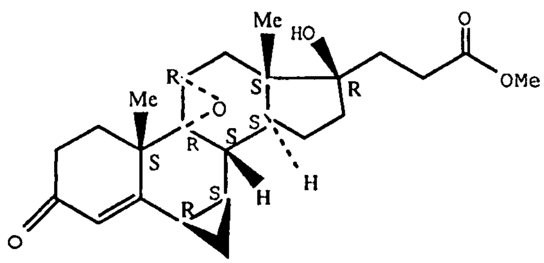
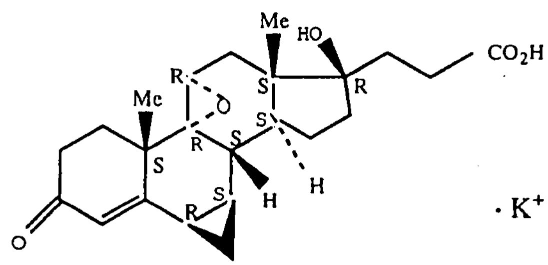
Compound #	Structure	Name
7		3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, methyl ester, (6α,7α,11α,17α)-
8		3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, monopotassium salt, (6α,7α,11α,17α)-

TABLE I: Aldosterone Receptor Antagonist

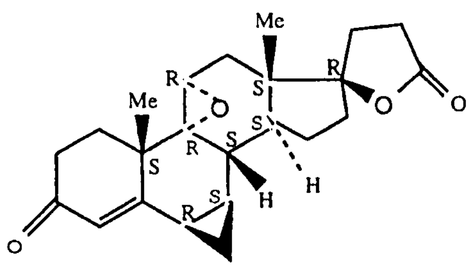
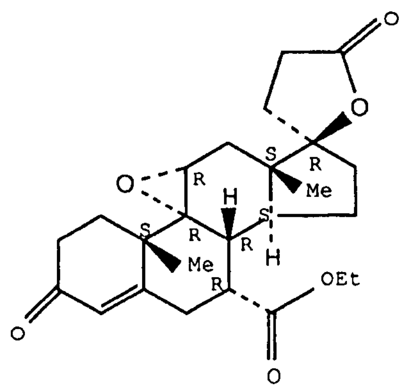
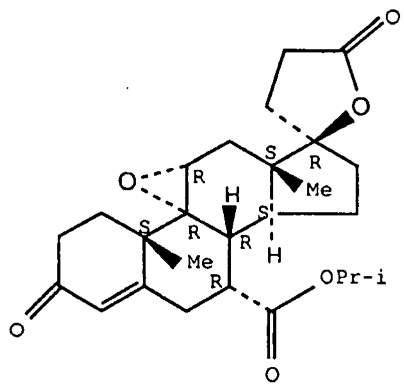
Compound #	Structure	Name
9		3'H-cyclopropa[6,7]pregna-1,4,6-triene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-,γ-lactone(6α,7α,11.α,17α)-
10		Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,γ-lactone, ethyl ester, (7α,11α,17α)-

TABLE I: Aldosterone Receptor Antagonist

Compound #	Structure	Name
11		Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,γ-lactone, 1-methylethyl ester (7α,11α,17α)-

Of particular interest is the compound eplerenone which is compound 1 as shown above. Eplerenone is an aldosterone receptor antagonist and has a higher specificity for aldosterone receptors than spironolactone. Selection of epleronone as the aldosterone antagonist in the present combination therapy likewise should be beneficial, yet diminish certain side effects such as gynecomastia.

A diuretic agent may be used with the combination of ACE inhibitor and aldosterone antagonist. Such diuretic agent may be selected from several known classes, such as thiazides and related sulfonamides, potassium-sparing diuretics, loop diuretics and organic mercurial diuretics. The term diuretic is not intended to embrace spirolactone-type compounds.

Examples of thiazides are bendroflumethiazide, benzthiazide, chlorothiazide, cyclothiazide, hydrochlorotthiazide, hydroflumethiazode, methyclothiazide, polythiazide and trichlormethiazide.

Examples of related sulfonamides are chlorthalidone, quinethazone and metolazone.

An example of a non-thiazide sulfonamide diuretic is metolazone.

Examples of potassium-sparing diuretics are triameterene and amiloride.

Examples of loop diuretics, i.e., diuretics acting in the ascending limb of the loop of Henle of the kidney, are furosemide and ethynacrylic acid.

Examples of organic mercurial diuretics are mercaptomerin sodium, merethoxylline procaine and mersalyl with theophylline.

Biological Evaluation

Human Clinical Trials

A combination therapies comprising two or more of the agents or compounds selected from the group consisting of ACE inhibitors, spironolactone, digoxin, and loop diuretics was evaluated in humans as described in the following clinical trials. The use of the term "placebo" is intended to embrace therapy which includes cardiovascular treatments described herein in the absence of spironolactone.

Patients: One thousand six hundred and sixty-three (1,663) patients with severe heart failure were enrolled in the study. Patients were eligible for enrollment in the study if they had a history of New York Heart Association (NYHA) Class IV heart failure within 6 months but no less than 6 weeks from randomization, and were NYHA Class III or IV at the time of enrollment. Eligible patients had a left ventricular ejection fraction of ≤35 percent and were to be receiving treatment with an angiotensin-converting enzyme inhibitor, if tolerated, and a loop diuretic. Treatment with digitalis and vasodilators was allowed, but potassium-sparing diuretics were not permitted. Oral potassium supplements were not recommended unless hypokalemia (serum potassium <3.5 mmol per liter) developed. A low salt diet (100-200 mEg/day, sodium) was recommended to all patients. Patients were excluded from the trial if they had clinically significant

operable valvular disease (other than mitral or tricuspid regurgitation), congenital heart disease, unstable angina, primary hepatic failure, active malignancy, a heart transplant or were a candidate for heart transplantation, or any life threatening disease (other than heart failure). Other criteria for exclusion were a serum creatinine concentration >2.5 mg per deciliter (>220 μmol per liter) or a serum potassium concentration >5.0 mmol per liter. The protocol was approved by the Institutional Review Boards or Ethics Committees of all participating institutions. Written informed consent was obtained from all patients.

Study Design: After the initial evaluation, patients were randomly assigned in a double-blind fashion to receive either oral spironolactone (Aldactone®, Searle) 25 mg once daily or matching placebo, in addition to their usual medication(s). After 8 weeks of treatment, at the discretion of the investigator, study drug could be increased to 50 mg once daily if there were signs and/or symptoms of progression of heart failure without evidence of hyperkalemia. If at any time the patient developed hyperkalemia, the dose could be decreased to 25 mg every other day; however, the investigator was encouraged to first adjust concomitant medications. Follow-up evaluations were conducted every 4 weeks until Week 12, and then every 3 months thereafter until study completion. Clinical laboratory determinations, including serum potassium, creatinine, sodium and N-terminal pro-atrial natriuretic peptide, were performed at baseline at Weeks 1, 4, 5, 8, 12 and then every 3 months thereafter until study completion. For patients in whom the study drug was increased to 50 mg once daily, a serum potassium determination was also performed at Week 9. Study medication could be withheld

for serious hyperkalemia (potassium ≥6.0 mmol per liter), serum creatinine >4.0 mg per deciliter (354 μmol per liter), intercurrent illness, or any conditions deemed medically necessary to protect the patient's best interest. However, all parties remained in the study to track hospitalizations and deaths.

A health-related quality of life questionnaire was also completed by patients at various intervals during the trial.

An independent Data and Safety Monitoring Board met periodically to review the unblinded results and an events committee adjudicated the cause of death and hospitalizations in a blinded fashion.

End Points: The primary end point of the study was total all-cause mortality. Secondary end points included cardiac mortality, incidence of cardiac hospitalization, the combined incidence of cardiac mortality plus hospitalization, and changes in NYHA class. The effect of spironolactone was also assessed in subgroups of patients defined on the basis of the following six pre-randomization variables: ejection fraction, etiology of heart failure, serum creatinine concentration, age, angiotensin-converting enzyme inhibitor type and dose, and digitalis use.

Statistical Analysis: Analysis of all-cause mortality (the primary end point) included all patients randomized, according to the randomly assigned treatment group based on the intention-to-treat principle. Kaplan-Meier methods were used to construct cumulative survival curves for the two treatment groups. The primary comparison between the two groups was based on a

log-rank test; Cox proportional-hazards regression models were developed to explore the effects of baseline variables on the estimated effect of spironolactone. Formal assessment of efficacy in this trial used a group sequential monitoring plan with a Lan-DeMets alpha-spending approach and an O'Brien-Fleming spending function.

The sample size was calculated (using a method developed by Lakatos) on the basis of the following assumptions: annual mortality rate in the placebo group would be 38 percent; the risk of death by would be reduced by 17 percent in the spironolactone group; and approximately 5 percent of the participants in the spironolactone group would stop study medication each year. The power to detect a difference between treatment groups under these assumptions was set at 90 percent (alpha-level of 0.05 by a two-tailed test).

The Data Safety Monitoring Board reviewed the accruing data from this trial for evidence of efficacy and safety, and at each meeting calculated the projected cumulative Type I error spent for efficacy. Since two large trials in heart failure had shown decidedly non-exponential distributions of time to death, the computations for group sequential monitoring of all-cause mortality were based on life-table calculations to project event rates. The critical z-value for declaring statistically significant efficacy of treatment planned at the end of the trial was 2.02, corresponding to a p-value of 0.043.

Recruitment: In total, 1,663 patients were enrolled from 195 centers in 15 countries.

Patient Characteristics: Patient demographic, vital signs, and cardiac status at baseline are summarized in Table 1A and Table 1B. Data presented in Table 1B have been audited, updated, and revised relative to Table 1A.

In total, 1,633 patients from 195 centers (15 countries) were enrolled in the trial; 841 were randomized to placebo and 822 to spironolactone. As shown in Table 1A and 1B, the baseline characteristics were similar for patients randomized to placebo and spironolactone. There were 8 patients (3 placebo, 5 spironolactone) that had history of NYHA Class IV, but were not Class III or IV at the time of randomization. Reasons for discontinuation of study medication are shown in Table 2A. During the trial, 17 patients were withdrawn from study medication due to cardiac transplantation, 7 in the spironolactone group and 10 in the placebo group; one patient from the placebo group died 4 days after cardiac transplantation. Patients who discontinued study medication were followed by regularly scheduled follow-up telephone contact for determination of vital status. After a mean follow-up of 24 months, the average dose of study medication was 32.12 mg for placebo and 26.75 mg for spironolactone.

Table 1A. Baseline Characteristics

Characteristics	Placebo (n=841)	Spironolactone (n=822)	Total (n=1663)
Age(yr)	65.1 ± 12	65.2 ± 12.1	65.1 ± 12
Race			
Caucasian	86%	87%	87%
Sex			
Male	614(73%)	603(73%)	1217(73%)
Female	227(27%)	219(27%)	446(27%)
Blood Pressure (mm Hg)			
Systolic	122 ± 20	123 ± 21	122 ± 20
Diastolic	75 ± 11	75 ± 12	75 ± 12
Heart Rate(beats/min)	81.1 ± 14.8	81 ± 14	81 ± 14
New York Heart Association Class			
II	3(0%)	5(1%)	8(0%)
III	581(69%)	591(72%)	1172(70%)
IV	257(31%)	226(27%)	483(29%)
Left Ventricular Ejection Fraction(%)	25.2 ± 6.8	25.6 ± 6.7	25.4 ± 6.7
Cause of Heart Failure			
Ischemic	453(54%)	454(55%)	907(55%)
Non-ischemic	386(46%)	368(45%)	754(45%)
Medication(% of Patients)			
Loop Diuretic	94%	99%	96%
ACE Inhibitor	88%	89%	89%
Digitalis	71%	73%	72%
Aspirin	38%	33%	35%
Potassium Supplements	24%	25%	25%
Beta Blockers	7%	7%	7%
Dose of ACE-Inhibitor(mg/day)			
Dose of Captopril	62.1	63.4	62.7
Dose of Enalapril	16.5	13.5	15.0
Dose of Lisinopril	13.1	15.5	14.4

TABLE 1B. BASE-LINE CHARACTERISTICS OF THE PATIENTS*

Characteristic	Placebo Group (*n*=841)	Spironolactone Group (*n*=822)
Age - yr	65 ± 12	65 ± 12
White race - %	86%	87%
Sex - no. (%)		
Male	614(73%)	603(73%)
Female	227(27%)	219(27%)
Blood Pressure - mm Hg		
Systolic	122 ± 20	123 ± 21
Diastolic	75 ± 11	75 ± 12
Heart Rate -beats/min	81± 15	81 ± 14
New York Heart Association Class - no. (%)		
II	3(0.4)	4(0.5)
III	581(69)	592(72)
IV	257(31)	226(27)
Left ventricular ejection fraction-%†	25.2 ± 6.8	25.6 ± 6.7
Cause of heart failure - no. (%)‡		
Ischemic	453(54%)	454(55%)
Non-ischemic	386(46%)	368(45%)
Medications - %		
Loop diuretics	100%	100%
ACE inhibitors	94%	95%
Digitalis	72%	75%
Aspirin	37%	36%
Potassium supplements	27%	29%
Beta-blockers	10%	11%
Mean dose of ACE inhibitor - mg/day		
Captopril	62.1	63.4
Enalapril	16.5	13.5
Lisinopril	13.1	15.5

* Plus-minus values are means ±SD. ACE denotes angiotensin-converting enzyme.

† The ejection fraction could be measured by contrast ventriculography, gated radionuclide ventriculography, or echocardiography.

‡ The cause of heart failure was determined on the basis of a patient's history, angiographic evidence, or both. Data on the cause of heart failure were not available for two patients in the placebo group.

Table 2A. Treatment Discontinuation

	Placebo	Spironolactone
Patients Enrolled	841	822
Death	351 (42%)	269 (33%)
Discontinued Therapy During Study	137 (16%)	134 (16%)
Treatment Failure	25 (3%)	9 (1%)
Adverse Effects	29 (3%)	51 (6%)
Heart Transplants	10 (1%)	7 (1%)
Non-Compliance/Physician's Choice	75 (9%)	67 (8%)

Effect of Spironolactone on Survival (See Fig. 1A, Fig 1B, and Fig. 2):

Among the 1,663 patients randomized, there were 351 deaths (41.7 percent) in the placebo group and 269 deaths (32.7 percent) in the spironolactone group; this difference represents an estimated 26 percent decrease in the risk of death by Cox proportional-hazards model (95 percent confidence interval, 13 to 37 percent; $p < 0.00001$) in patients randomized to spironolactone (Fig. 1A and 1B). Data presented in Figure 1B have been audited, updated, and revised relative to Figure 1A. Preliminary analysis based upon investigator initiated (unadjudicated) case report forms suggests that the reduction in mortality observed with spironolactone was due to decreases in both progressive heart failure and sudden death.

Data after careful audit and update were revised as shown in Fig. 1B, Table 2B, Fig. 4, and Table 2C. There were 386 deaths in the placebo group (46 percent) and 284 deaths in the spironolactone group (35 percent), representing a 30 percent reduction in the risk of death (relative risk of death among the patients in the spironolactone group, 0.70 by a Cox proportional-hazards model; 95 percent confidence interval, 0.60 to 0.82; $P<0.001$). A total of 314 deaths in the placebo group (37 percent) and 226 deaths in the spironolactone group (27 percent) were attributed to cardiac causes, representing a 31 percent reduction in the risk of death from cardiac causes (relative risk, 0.69; 95 percent confidence interval, 0.58 to 0.82; $P<0.001$). The reduction in the risk of death among the patients in the spironolactone

group was attributed to significantly lower risks of both death from progressive heart failure and sudden death from cardiac causes.

The reduction in the risk of death among patients in the spironolactone group was analyzed in each of six prespecified subgroups as well as in retrospective analyses performed according to sex, NYHA class, baseline serum potassium concentration, use of potassium supplements, and use of beta-blockers. Fig. 4, Table 2C, Fig. 5-9. The estimated beneficial effect was similar across geographic regions.

During the trial, 336 patients in the placebo group and 260 patients in the spironolactone group were hospitalized at least once for cardiac reasons (Table 2B). In total, there were 753 hospitalizations for cardiac causes in the placebo group and 515 in the spironolactone group, representing a 30 percent reduction in the risk of hospitalization for cardiac causes among patients in the spironolactone group (relative risk, 0.70; 95 percent confidence interval, 0.59 to 0.82; P<0.001)(Table 2B). Analysis of the combined end point of death from cardiac causes or hospitalization for cardiac causes revealed a 32 percent reduction in the risk of this end point among patients in the spironolactone group as compared with those in the placebo group (relative risk, 0.68; 95 percent confidence interval, 0.59 to 0.78; P<0.001) (Table 2C).

The reduction in mortality in patients randomized to spironolactone was demonstrated regardless of age, sex, etiology of heart failure, NYHA functional class III or IV, digitalis use, baseline serum potassium or creatinine levels. There was a trend toward a greater

reduction in mortality in spironolactone-treated patients with baseline ejection fractions ≥27 (Fig. 4-10).

Effect of Spironolactone on Non-Fatal Hospitalizations (See Fig. 3):

During the trial, 510 (61 percent) placebo-treated and 445 (54 percent) spironolactone-treated patients had at least one non-fatal hospitalization, representing 1,595 hospitalizations for the placebo group and 1,347 hospitalizations for the spironolactone group. Using the Cox proportional-hazards model for the combined end point analysis of total non-fatal hospitalization and total all-cause mortality, we observed a 20 percent risk reduction in the spironolactone group compared to the placebo group (95 percent confidence interval of 10 to 29 percent, p=0.00017)(Fig.3).

TABLE 2B. RELATIVE RISKS OF DEATH AND HOSPITALIZATION

Variable	Placebo Group (N=841)	Spironolactone Group (N=822)	Relative Risk (95% CI)*	P Value
	no. of patients			
Cause of death				
Cardiac causes	314	226	0.69(0.58-0.82)	<0.001
Progression of heart failure†	189	127	0.64(0.51-0.80)	<0.001
Sudden death‡	110	82	0.71(0.54-0.95)	0.02
Myocardial infarcation	15	17		
Other cardiovascular causes	13	12		
Stroke	11	8		
Noncardiovascular causes	41	29		
Unknown	7	9		
Total	386	284	0.70(0.60-0.82)	<0.001
	no. of patients/no. of events			
Reason for hospitalization				
Cardiac causes§	336/753	260/515	0.70(0.59-0.82)	<0.001
Worsening heart failure	300/663	215/413	0.65(0.54-0.77)	<0.001
Angina	35/44	43/66		
Ventricular arrhythmias	24/31	23/25		
Myocardial infarction	14/15	10/11		
Other cardiovascular causes	112/163	117/169		
Stroke	20/24	14/15		
Noncardiovascular causes	232/377	223/361		

TABLE 2C. RELATIVE RISKS OF THE COMBINED END POINTS OF DEATH OR HOSPITALIZATION IN THE SPIRONOLACTONE GROUP

END POINT	Relative Risk (95% CI)	P Value
Death from cardiac causes or hospitalization for cardiac causes	0.68(0.59-0.78)	<0.001
Death from any cause or hospitalization for any reason	0.77(0.68-0.86)	<0.001
Death from any cause or hospitalization for cardiac causes	0.68(0.60-0.77)	<0.001

<u>Effect of Spironolactone on Changes of NYHA Functional Class: (See Table 3)</u>

Three categories were used to assess changes in the symptoms of heart failure: improvement, no change, and worsening or death. The condition of patients who were in NYHA class III at base line was considered to have improved if they were in NYHA class I or II at the end of the study and considered to have worsened if they were in NYHA class IV (or had died). The condition of patients who were in NYHA class IV at base line was considered to have improved if they were in NYHA class I, II, or III at the end of the study; other patients in NYHA class IV at base line either had no change at the end of the study or died. Using the Cochran-Mantel-Haenszl test for association between drug therapy and NYHA class outcome (worse, same, improvement), there was a significant improvement from the baseline NYHA functional class in the spironolactone group compared to the placebo group (p=0.001). In the placebo group, the condition of 33 percent of the patients improved; it did not change in 18 percent, and it worsened in 48 percent. In the spironolactone group, the condition of 41 percent of the patients improved; it did not change in 21 percent, and it worsened in 38 percent. The difference between groups was significant (P<0.001 by the Wilcoxon test). As shown in Fig. 6, 7, and 9, spironolactone co-therapy resulted in a total reduction in mortality in patients who were classified as Class III and Class IV upon entry to this study.

Table 3. NYHA Class Changes

	Placebo	Aldactone
Class III	(n=581)	(n=591)
Worse (Class IV + Death)	227 (39%)	189 (32%)
No Change	176 (30%)	186 (31%)
Improvement	178 (31%)	216 (37%)
Class IV	(n=257)	(n=226)
Death	134 (52%)	96 (42%)
No Change	31 (12%)	26 (12%)
Improvement	92 (36%)	104 (46%)

Safety:

Changes in serum potassium, serum creatinine, blood pressure, and heart rate are shown in Table 4. There were no significant differences between the two groups in serum sodium concentration, blood pressure, or heart rate during the study. The median creatinine and potassium concentrations did not change in the placebo group during the first year of follow-up, the period for which the data were most complete. During the same period, however, the median creatinine concentration in the spironolactone group increased by approximately 0.05 to 0.10 mg per deciliter (4 to 9 μmol per liter) and the median potassium concentration increased by 0.30 mmol per liter. The differences between the two groups were significant (P<0.001) but were not clinically important. The most frequent adverse reactions are listed in Table 5A. Gynecomastia and breast pain in males was reported in 9 patients (1.5 percent) in the placebo group compared to 51 patients (8.5 percent) in the spironolactone group, (p<0.0001). Serious hyperkalemia occurred in 10 patients (1.2 percent) in the placebo

group compared to 14 patients (1.7 percent) in the spironolactone group. One patient discontinued therapy due to hypotension in the placebo group, and none in the spironolactone group.

Data presented in Table 5B have been audited, updated, and revised relative to Table 5A. Table 5B shows that serious hyperkalemia occurred in 10 patients in the placebo group (1 percent) and 14 patients in the spironolactone group (2 percent, P=0.42). Gynecomastia or breast pain was reported by 10 percent of the men in the spironolactone group and 1 percent of the men in the placebo group (P<0.001), causing more patients in the spironolactone group than in the placebo group to discontinue treatment (10 vs. 1, P=0.006).

TABLE 4. Changes in Serum Potassium and Creatinine, Blood Pressure and Heart Rate

	Baseline	Wk 4	Wk 8	Wk 12	Mth 6	Mth 9	Mth 12	Mth 18	Mth 24
Serum Potassium (mmol/Lt.)									
Placebo	4.24	4.28	4.25	4.25	4.26	4.28	4.28	4.22	4.34
Spiro	4.21	4.54	4.53	4.58	4.56	4.54	4.52	4.59	4.52
Serum Creatinine (mmol/Lt.)									
Placebo	110	110	110	109	111	111	111	111	110
Spiro	109	115	114	116	116	117	115	113	113
Heart Rate (beats/minute)									
Placebo	81	81	80	80	78	79	77	78	78
Spiro	81	80	79	79	78	78	78	78	78
Systolic Blood Pressure (mm/Hg)									
Placebo	122	122	123	124	125	125	126	125	124
Spiro	123	121	122	121	123	124	123	125	122
Diastolic Blood Pressure (mm/Hg)									
Placebo	75	75	75	75	75	75	75	74	73
Spiro	75	74	73	73	74	74	74	74	77

Table 5A. Most Frequent Adverse Reactions

Adverse Reaction	Placebo (n=841)	Aldactone (n=822)
	No. of Patients (%)	
Patients with one or more events	677 (80)	649 (79)
Patients with no adverse events	164 (20)	173 (21)
Cardiovascular disorder	375 (45)	344 (42)
Progression Heart Failure	167 (20)	134 (16)
Angina	84 (10)	91 (11)
Palpitation	33 (4)	35 (4)
Respiratory Disorder	386 (46)	340 (41)
Dyspnea	231 (27)	194 (24)
Cough	105 (12)	96 (12)
Upper respiratory infection	108 (13)	114 (14)
Pneumonia	18 (2)	10 (1)
Pulmonary edema	33 (4)	23 (3)
Neoplasm	4 (<1)	4 (<1)
Urinary system disorder	71 (8)	75 (9)
Skin and appendages disorder	69 (8)	64 (8)
Musculoskeletal disorder	104 (12)	96 (12)
Nervous system disorder	156 (19)	175 (21)
Psychiatric disorder	113 (13)	110 (13)
Gastrointestinal disorder	208 (25)	210 (26)
Endocrine disorder	20 (2)	65 (8)
Gynecomastia (male)	8 (1)	43 (7)*
Breast pain (male)	1 (<1)	8 (1)
Edema	56 (7)	49 (6)
Serious hyperkalemia	10 (1.2)	14 (1.7)
Discontinuation due to hypertension	56 (7)	0 (0)

*p<0.0001

TABLE 5B. ADVERSE EVENTS

Adverse Event	Placebo Group (N=841)	Spironolactone Group (N=822)
	no. of patients(%)	
One or more events	667(79%)	674(82)*
Discontinuation because of adverse event	40(5)	62(8)
Cardiovascular disorders	251(30)	248(30)
Angina	83(10)	103(13)
Heart failure	80(10)	52(6)
Respiratory tract disorders	285(34)	262(32)
Cough	117(14)	103(13)
Dyspnea	39(5)	34(4)
Pneumonia	25(3)	17(2)
Pulmonary edema	7(0.8)	5(0.6)
Pleural effusion	11(1)	3(0.4)
Metabolic and nutritional disorders	215(26)	269(33)
Hyperuricemia	25(3)	16(2)
Neoplasm	10(1)	13(2)
Urinary system disorders	89(11)	99(12)
Disorders of skin and appendages	72(9)	73(9)
Musculoskeletal disorders	118(14)	101(12)
Nervous system disorders	173(21)	185(23)
Psychiatric disorders	126(15)	122(15)
Gastrointestinal disorders	241(29)	236(29)
Endocrine disorders	26(3)	84(10)
Gynecomastia in men†	8(1)	55(9)‡
Breast pain in men‡	1(0.1)	10(2)§
Gynecomastia or breast pain in men†	9(1)	61(10)‡
Edema	21(2)	18(2)
Serious hyperkalemia	10(1)	14(2)

Effect of Spironolactone on PIIINP and Mortality

A sample of 253 patients from within the study group participated in a substudy (CHF NYHA III and IV, mean age 69, left ventricular ejection fraction ("LVEF") =26%, ischemic heart disease=46%, all were on conventional therapy, 92% on ACE inhibitors). Patients were randomized to placebo or spironolactone 15.5 to 50 mg/day. Serum PIIINP was measured at baseline and 6 months after randomization. Mean survival was 24 months.

Baseline serum PIIINP level was 4.6 (s.d.=2.5) and was similar in the spironolactone and placebo group. At 6 months, PIIINP decreased in the spironolactone from 4.9 (s.d.=2.7) to 4.1 (s.d.=1.9)(p=0.005), but not in the placebo group (p=0.65). Baseline levels above the 95% CL of controls (>4.2 μg/l) were associated with an increased risk of death in the placebo group (RR=1.89 [1.12-3.2](p=0.01)), but not in the spironolactone group (RR=0.69[0.45-1.36](p=0.39)). More marked survival benefit of spironolactone treatment was observed in patients with a baseline PIIINP > 4.2 μg/l as compared to patients with lower baseline levels of PIIINP (RR=0.54 [0.33-0.88](p<0.02) vs. 1.37 [0.78-2.31](p=0.28). The mortality relative risk reduction was 33% in the high risk group. These findings were

unchanged after adjustment for other prognostic factors (NYHA class, serum creatinine and age).

It is suggested by these studies that in patients with CHF, elevated serum PIIINP was significantly associated with excess mortality. Spironolactone decreased serum PIIINP and suggested that the beneficial effect of spironolactone on survival in patients with CHF may be explained, in part, by the lowering extracellular matrix production or turnover.

Spironolactone Effect to Lower Brain Natriuretic Peptide Levels is Associated with Reduced Risk of Mortality

A sample of 107 patients from within the study group group participated in a substudy (NYHA III-IV), mean LVEF 25%). Patients received standard CHF therapy and 25 mg/day spironolactone or placebo. Brain Natriuretic Peptide (BNP) levels were measured at baseline and 3 and 6 months after therapy. Results were expressed in pg/ml, geometric mean [95%CL] and data were compared using a Mann-Whitney-Wilcoxon test.

Table 6: Effect of Spironolactone on BNP levels

	Placebo (n=53)	Spironolactone (n=54)	p value
To	74 [64-85]	67 [59-76]	0.33
T3	68 [49-78]	52 [45-61]	0.02
T6	64 [54-76]	52 [44-61]	0.09
T3/T0	0.99	0.77	0.004
T6/T0	0.96	0.77	0.05

Thus, Spironolactone treatment, which results in a significant decrease in fatalities and non-fatal hospitalizations, also results in a decrease in BNP levels and may reflect the beneficial effect on the left ventricular remodeling though the reduction of myocardial stretching.

Table 7: Relative Risk of Reduction in Mortality Analyzed by Baseline Characteristics

Patients	Risk Reduction with Spironolactone	Significance
LVEF of $\leq$ 21%	25%	$p=0.034$
LVEF 22-29%	26%	$p=0.020$
LVEF 30-50%	37%	$p=0.011$
NYHA Class III heart failure	28%	$p<0.0008$
NYHA Class IV heart failure	29%	$p<0.0098$
ischemic heart failure	28%	$p<0.0012$
nonischemic heart failure	32%	$p<0.0016$

Dosing based on Natriuretic peptides and PIIINP

The natriuretic peptides are a group of structurally similar but genetically distinct peptides that have diverse actions in cardiovascular, renal, and endocrine homeostasis. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are of myocardial

cell origin and C-type natriuretic peptide (CNP) is of endothelial origin. ANP and BNP bind to the natriuretic peptide-A receptor (NPR-A), which, via 3',5'-cyclic guanosine monophosphate (cGMP), mediates natriuresis, vasodilation, renin inhibition, antimitogenesis, and lusitropic properties.

ANP is thought to play a role in renal regulation of salt balance by reducing tubular reabsorption of sodium and chloride. ANP can excite cardiac nerve endings and invoke a decrease in arterial blood pressure and a reduction in renal sympathetic nerve activity. Congestive heart failure represents a pathological state in which the activation of the natriuretic peptides exceeds those of all other states and is associated with poor long-term prognosis in heart failure.

Atrial natriuretic factor (ANF) production is induced in the ventricle under pathological circumstances and after exposure to hypertrophic agents including the α-adrenergic agonist phenylephrine. Release of ANF is significantly under conditions of hypertension and infarction. Even though ventricular natriuretic factor (ANF) has been considered to be a specific molecular marker of hypertrophy, its role in hypertrophy is unclear. Levin, E. R., Gardner, D. G., and Samson, W. K. (1998) *N. Engl. J. Med.* 339, 321-328

Extracellular matrix turnover is one of the determinants of vascular constrictive remodeling and may be monitored by measuring the blood level of procollagen type III aminoterminal propeptide ("PIIINP"). In congestive heart failure, extracellular matrix turnover is a major determinant of cardiac remodeling, diastolic function and pumping capacity.

Accordingly, dosing of therapeutic agents for congestive heart disease may be determined and adjusted based on measurement of blood concentrations of PIIINP, ANF, ANP, or BNP. A decrease in blood PIIINP level relative to baseline PIIINP level prior to administration of the aldosterone antagonist and during administration indicate a decrease in extracellular matrix turnover and therefore provides a correlation with inhibition of congestive heart disease. Similarly, levels of ANF, ANP, and BNP and may be relative to baseline levels prior to administration of the aldosterone antagonist and during administration to indicate levels of efficacy.

Administration of the angiotensin converting enzyme inhibitor and the aldosterone antagonist may take place sequentially in separate formulations, or may be accomplished by simultaneous administration in a single formulation or separate formulations. Administration may be accomplished by oral route, or by intravenous, intramuscular or subcutaneous injections. The formulation may be in the form of a bolus, or in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more pharmaceutically-acceptable carriers or diluents, or a binder such as gelatin or hydroxypropyl-methyl cellulose, together with one or more of a lubricant, preservative, surface-active or dispersing agent.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a

dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The ACE inhibitor may be present in an amount from about 1 to 200 mg, preferably from about 2 to 150 mg, depending upon the specific ACE inhibitor selected. A suitable daily dose for a mammal may vary widely depending on the condition of the patient and other factors. The ALDO antagonist may be present in an amount of from about 1 to 400 mg, preferably from about 2 to 150 mg, depending upon the specific ALDO antagonist compound selected and the specific disease state being targeted for the combination therapy.

For disease states which require prevention, reduction or treatment of a cardiovascular disease state without incidence of hyperkalemia, for example, the ALDO antagonist component, typically spironolactone, will be present in the combination therapy in an amount in a range from about 1 mg to about 25 mg per dose per day.

Examples of various fixed combinations of ACE inhibitor and ALDO antagonist representing a "double therapy" of the invention are as follows:

ACE Inhibitor			ALDO Antagonist
Captopril(mg)[1]	Enalapril(mg)[1]	Lisinopril(mg)[2]	Spironolactone (mg)[2]
7.5 to 30	2.5 to 20	5 to 20	5
7.5 to 30	2.5 to 20	5 to 20	7.5
7.5 to 30	2.5 to 20	5 to 20	10
7.5 to 30	2.5 to 20	5 to 20	12.5
7.5 to 30	2.5 to 20	5 to 20	15
7.5 to 30	2.5 to 20	5 to 20	17.5
7.5 to 30	2.5 to 20	5 to 20	20
7.5 to 30	2.5 to 20	5 to 20	22.5
7.5 to 30	2.5 to 20	5 to 20	25
7.5 to 30	2.5 to 20	5 to 20	50

[1]Dose given 2 times per day
[2]Dose given once per day

The present invention further comprises a composition comprising an angiotensin converting enzyme inhibitor, an aldosterone antagonist, a loop diuretic and digoxin, and the pharmaceutically acceptable salts, esters and prodrugs thereof. Preferably, the composition comprises a first amount of an angiotensin converting enzyme inhibitor, or a pharmaceutically acceptable salt, ester or prodrug thereof; a second amount of an aldosterone antagonist, or a pharmaceutically acceptable salt, ester or prodrug thereof; a third amount of a loop diuretic, or a pharmaceutically acceptable salt, ester or prodrug thereof; a fourth amount of digoxin, or a pharmaceutically acceptable salt, ester or prodrug thereof; and a pharmaceutically acceptable carrier; wherein the first, second, third and fourth amounts in

combination comprise a therapeutically effective amount of said inhibitor, antagonist, loop diuretic and digoxin. More preferably, the aldosterone antagonist is selected from spironolactone and eplerenone.

The active ingredients may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

The dosage regimen for treating a disease condition with the combination therapy of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex and medical condition of the patient, the severity of the disease, the route of administration, and the particular compound employed, and thus may vary widely.

For therapeutic purposes, the active components of this combination therapy invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered _per os_, the components may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be

prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The components may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Pharmaceutical compositions for use in the treatment methods of the invention may be administered in oral form or by intravenous administration. Oral administration of the combination therapy is preferred. Dosing for oral administration may be with a regimen calling for single daily dose, or for a single dose every other day, or for multiple, spaced doses throughout the day. The active agents which make up the combination therapy may be administered simultaneously, either in a combined dosage form or in separate dosage forms intended for substantially simultaneous oral administration. The active agents which make up the combination therapy may also be administered sequentially, with either active component being administered by a regimen calling for two-step ingestion. Thus, a regimen may call for sequential administration of the active agents with spaced-apart ingestion of the separate, active agents. The time period between the multiple ingestion steps may range from a few minutes to several hours, depending upon the properties of each active agent such a potency, solubility, bioavailability, plasma half-life and kinetic profile of the agent, as well as depending upon the age and condition of the patient. The active agents of the combined therapy whether administered

simultaneously, substantially simultaneously, or sequentially, may involve a regimen calling for administration of one active agent by oral route and the other active agent by intravenous route. Whether the active agents of the combined therapy are administered by oral or intravenous route, separately or together, each such active agent will be contained in a suitable pharmaceutical formulation of pharmaceutically-acceptable excipients, diluents or other formulations components. Examples of suitable pharmaceutically-acceptable formulations containing the active components for oral administration are given below. Even though such formulations list both active agents together in the same recipe, it is appropriate for such recipe to be utilized for a formulation containing one of the active components.

Example 1

An oral dosage may be prepared by screening and then mixing together the following list of ingredients in the amounts indicated. The dosage may then be placed in a hard gelatin capsule.

Ingredients	Amounts
captopril	62.0 mg
spironolactone	12.5 mg
magnesium stearate	10 mg
lactose	100 mg

Example 2

An oral dosage may be prepared by mixing together and granulating with a 10% gelatin solution. The wet granules are screened, dried, mixed with starch, talc

and stearic acid, screened and compressed into a tablet.

Ingredients	Amounts
captopril	62.0 mg
spironolactone	12.5 mg
calcium sulfate dihydrate	100 mg
sucrose	15 mg
starch	8 mg
talc	4 mg
stearic acid	2 mg

Example 3

An oral dosage may be prepared by screening and then mixing together the following list of ingredients in the amounts indicated. The dosage may then be placed in a hard gelatin capsule.

Ingredients	Amounts
enalapril	15 mg
spironolactone	12.5 mg
magnesium stearate	10 mg
lactose	100 mg

Example 4

An oral dosage may be prepared by mixing together and granulating with a 10% gelatin solution. The wet granules are screened, dried, mixed with starch, talc and stearic acid, screened and compressed into a tablet.

Ingredients	Amounts
enalapril	15 mg
spironolactone	12.5 mg
calcium sulfate dihydrate	100 mg
sucrose	15 mg
starch	8 mg
talc	4 mg
stearic acid	2 mg

Example 5

An oral dosage may be prepared by screening and then mixing together the following list of ingredients in the amounts indicated. The dosage may then be placed in a hard gelatin capsule.

Ingredients	Amounts
lisinopril	15 mg
spironolactone	12.5 mg
magnesium stearate	10 mg
lactose	100 mg

Example 6

An oral dosage may be prepared by mixing together and granulating with a 10% gelatin solution. The wet granules are screened, dried, mixed with starch, talc and stearic acid, screened and compressed into a tablet.

Ingredients	Amounts
lisinopril	15 mg
spironolactone	12.5 mg
calcium sulfate dihydrate	100 mg
sucrose	15 mg
starch	8 mg
talc	4 mg
stearic acid	2 mg

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

Example 7

An oral dosage may be prepared by screening and then mixing together the following list of ingredients in the amounts indicated. The dosage may then be placed in a hard gelatin capsule.

Ingredients	Amounts
lisinopril	15 mg
spironolactone	12.5 mg
furosemide	73.9 mg
magnesium stearate	10 mg
lactose	100 mg

Example 8

An oral dosage may be prepared by screening and then mixing together the following list of ingredients in the amounts indicated. The dosage may then be placed in a hard gelatin capsule.

Ingredients	Amounts
lisinopril	15 mg
spironolactone	12.5 mg
furosemide	73.9 mg
digoxin	75 µg
magnesium stearate	10 mg
lactose	100 mg

All mentioned references are incorporated by reference as if here written. When introducing elements of the present invention or the preferred embodiment(s) thereof, the articles "a", "an", "the" and "said" are intended to mean that there are one or more of the elements. The terms "comprising", "including" and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

What Is Claimed Is:

1. A co-therapy for treating a cardiovascular disorder in a subject, wherein said co-therapy comprises administering a therapeutically-effective amount of an angiotensin converting enzyme inhibitor and administering an aldosterone antagonist in an amount therapeutically effective to antagonize aldosterone to reduce the death rate or the number of non-fatal hospitalizations as compared to monotherapy with an angiotensin converting enzyme inhibitor.

2. The co-therapy of Claim 1 further characterized by administering said angiotensin converting enzyme inhibitor and said aldosterone antagonist in a sequential manner.

3. The co-therapy of Claim 1 further characterized by administering said angiotensin converting enzyme inhibitor and said aldosterone antagonist in a substantially simultaneous manner.

4. The co-therapy of Claim 1 wherein said aldosterone antagonist is a spirolactone-type compound.

5. The co-therapy of Claim 4 wherein said spirolactone-type compound is spironolactone.

6. The co-therapy of Claim 1 wherein said angiotensin converting enzyme inhibitor is selected from the group consisting of alacepril, benazepril, captopril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, fosinoprilat, imidapril, lisinopril, perindopril, quinapril, ramipril, saralasin acetate, temocapril, trandolapril, ceranapril, moexipril, quinaprilat, spirapril, Bioproject BP1.137, Chiesi CHF

1514, Fisons FPL-66564, idrapril, Marion Merrell Dow MDL-100240, perindoprilat and Servier S-5590.

7. The co-therapy of Claim 6 wherein said angiotensin converting enzyme inhibitor is selected from the group consisting of alacepril, benazepril, captopril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, fosinoprilat, imidapril, lisinopril, perindopril, quinapril, ramipril, saralasin acetate, temocapril, trandolapril, ceranapril, moexipril, quinaprilat and spirapril.

8. The co-therapy of Claim 1 further characterized by said angiotensin converting enzyme inhibitor and said aldosterone antagonist being used in said co-therapy in a weight ratio range from about 0.1-to-one to about twenty-five-to-one of said angiotensin converting enzyme inhibitor to said aldosterone antagonist.

9. The co-therapy of Claim 8 wherein said weight ratio range is from about 0.5-to-one to about fifteen-to-one.

10. The co-therapy of Claim 9 wherein said weight ratio range is from about 0.5-to-one to about five-to-one.

11. The co-therapy of Claim 9 wherein said angiotensin converting enzyme inhibitor is captopril, in a daily dose range from about 30 mg to about 80 mg per dose, or is enalapril in a dose range from about 5 mg to about 25 mg per dose.

12. The co-therapy of Claim 11 wherein said aldosterone antagonist is spironolactone in a daily dose range from about 1 mg to about 23 mg per dose.

13. The co-therapy of Claim 12 wherein said spironolactone daily dose is in a range from about 5 mg to about 20 mg.

14. The co-therapy of Claim 12 wherein said spironolactone daily dose is in a range from about 5 mg to about 15 mg.

15. A combination therapy for treating a cardiovascular disorder in a subject, wherein said combination therapy comprises administering an angiotensin converting enzyme inhibitor, an aldosterone antagonist and a loop diuretic to the subject, and wherein the angiotensin converting enzyme inhibitor, the aldosterone antagonist and the loop diuretic are administered at doses that in combination result in a statistically significant reduction in the death rate or the number of non-fatal hospitalizations as compared to said combination therapy without the aldosterone antagonist, and wherein said loop diuretic has no substantial aldosterone antagonistic effect.

16. A combination therapy for treating a cardiovascular disorder in a subject, wherein said combination therapy comprises administering an angiotensin converting enzyme inhibitor, an aldosterone antagonist and a loop diuretic to the subject, and wherein the angiotensin converting enzyme inhibitor, the aldosterone antagonist and the loop diuretic are administered at doses that in combination result in a statistically significant reduction in the death rate as

compared to said combination therapy without the aldosterone antagonist, and wherein said loop diuretic has no substantial aldosterone antagonistic effect.

17. A combination therapy for treating a cardiovascular disorder in a subject, wherein said combination therapy comprises administering an angiotensin converting enzyme inhibitor, an aldosterone antagonist and a loop diuretic to the subject, and wherein the angiotensin converting enzyme inhibitor, the aldosterone antagonist and the loop diuretic are administered at doses that in combination result in a statistically significant reduction in the number of non-fatal hospitalizations as compared to said combination therapy without the aldosterone antagonist, and wherein said loop diuretic has no substantial aldosterone antagonistic effect.

18. A combination therapy for treating a cardiovascular disorder in a subject, wherein said combination therapy comprises administering an angiotensin converting enzyme inhibitor, an aldosterone antagonist and a loop diuretic to the subject, and wherein the angiotensin converting enzyme inhibitor, the aldosterone antagonist and the loop diuretic are administered at doses that in combination result in a statistically significant reduction in the rate of deaths resulting from sudden death in subjects afflicted with or susceptible to elevated heart rate variability as compared to said combination therapy without the aldosterone antagonist, and wherein said loop diuretic has no substantial aldosterone antagonistic effect.

19. A combination therapy for treating a cardiovascular disorder in a subject, wherein said

combination therapy comprises administering an angiotensin converting enzyme inhibitor, an aldosterone antagonist and a loop diuretic to the subject, and wherein the angiotensin converting enzyme inhibitor, the aldosterone antagonist and the loop diuretic are administered at doses that in combination result in a statistically significant reduction in the death rate for deaths resulting from progression of heart failure as compared to said combination therapy without the aldosterone antagonist, and wherein said loop diuretic has no substantial aldosterone antagonistic effect.

20. A combination therapy for treating a cardiovascular disorder in a subject, wherein said combination therapy comprises administering an angiotensin converting enzyme inhibitor, an aldosterone antagonist and a loop diuretic to the subject, and wherein the angiotensin converting enzyme inhibitor, the aldosterone antagonist and the loop diuretic are administered at doses that in combination result in a statistically significant reduction in the death rate or the number of non-fatal hospitalizations in subjects having a left ventricular ejection fraction greater than about 26% as compared to said combination therapy without the aldosterone antagonist, and wherein said loop diuretic has no substantial aldosterone antagonistic effect.

21. A combination therapy for treating a cardiovascular disorder in a subject, wherein said combination therapy comprises administering an angiotensin converting enzyme inhibitor, an aldosterone antagonist and a loop diuretic to the subject, and wherein the angiotensin converting enzyme inhibitor, the aldosterone antagonist and the loop diuretic are

administered at doses that in combination result in a statistically significant reduction in the death rate or the number of non-fatal hospitalizations in subjects having a left ventricular ejection fraction less than about 26% as compared to said combination therapy without the aldosterone antagonist, and wherein said loop diuretic has no substantial aldosterone antagonistic effect.

22. A combination therapy for treating a cardiovascular disorder in a subject, wherein said combination therapy comprises administering an angiotensin converting enzyme inhibitor, an aldosterone antagonist and a loop diuretic to the subject, and wherein the angiotensin converting enzyme inhibitor, the aldosterone antagonist and the loop diuretic are administered at doses that in combination suppress clinically significant cough due to elevated pulmonary arterial fibrosis or low levels of pulmonary blood pressure in the subject as compared to said combination therapy without the aldosterone antagonist, and wherein said loop diuretic has no substantial aldosterone antagonistic effect.

23. The combination therapy of Claim 22 wherein the angiotensin converting enzyme inhibitor, aldosterone antagonist and loop diuretic are administered at doses that in combination result in a statistically significant reduction in the death rate or the number of non-fatal hospitalizations as compared to said combination therapy without the aldosterone antagonist.

24. A combination therapy for treating a cardiovascular disorder in a subject, wherein said combination therapy comprises administering a

therapeutically-effective amount of an angiotensin converting enzyme inhibitor, a therapeutically-effective amount of an aldosterone antagonist, a therapeutically-effective amount of a loop diuretic and a therapeutically-effective amount of digoxin to the subject.

25. The combination therapy of Claim 24 wherein the angiotensin converting enzyme inhibitor, aldosterone antagonist, loop diuretic and digoxin are administered at doses that in combination result in a statistically significant reduction in the death rate as compared to the combination therapy of Claim 16.

26. The combination therapy of Claim 24 wherein the angiotensin converting enzyme inhibitor, aldosterone antagonist, loop diuretic and digoxin are administered at doses that in combination result in a statistically significant reduction in the number of non-fatal hospitalizations as compared to the combination therapy of Claim 17.

27. The combination therapy of Claim 24 wherein the angiotensin converting enzyme inhibitor, aldosterone antagonist, loop diuretic and digoxin are administered at doses that in combination result in a decrease in blood N-terminal atrial natriuretic factor level in the subject as compared to the combination therapy of Claim 15.

28. The combination therapy of Claim 24 wherein the angiotensin converting enzyme inhibitor, aldosterone antagonist, loop diuretic and digoxin are administered at doses that in combination result in a decrease in blood procollagen type III aminoterminal propeptide

level in the subject as compared to the combination therapy of Claim 15.

29. The combination therapy of Claim 24 wherein the angiotensin converting enzyme inhibitor, aldosterone antagonist, loop diuretic and digoxin are administered at doses that in combination result in an increase in left ventricular ejection fraction in the subject as compared to the combination therapy of Claim 15.

30. The combination therapy of Claim 15 wherein the subject is a human.

31. The combination therapy of Claim 15 wherein the subject is susceptible to sudden death.

32. The combination therapy of Claim 15 wherein the subject is classified in New York Heart Association class III or class IV prior to combination therapy.

33. The combination therapy of Claim 15 wherein the subject has a left ventricular ejection fraction greater than about 26%.

34. The combination therapy of Claim 15 wherein the subject has a left ventricular ejection fraction less than about 26%.

35. The combination therapy of Claim 15 wherein the subject is susceptible to or suffering from clinically significant cough due to elevated pulmonary arterial fibrosis or low levels of pulmonary blood pressure.

36. The combination therapy of Claim 15 wherein the loop diuretic is selected from furosemide and ethynacrylic acid.

37. The combination therapy of Claim 15 further comprising the administration of a therapeutically-effective amount of digoxin.

38. The combination therapy of Claim 15 wherein the angiotensin converting enzyme inhibitor, aldosterone antagonist and loop diuretic are administered at doses that in combination result in a decrease in blood N-terminal atrial natriuretic factor level in the subject as compared to the combination therapy of Claim 15.

39. The combination therapy of Claim 15 wherein the angiotensin converting enzyme inhibitor, aldosterone antagonist and loop diuretic are administered at doses that in combination result in a decrease in blood procollagen type III aminoterminal propeptide level in the subject as compared to the combination therapy of Claim 15.

40. The combination therapy of Claim 15 wherein the angiotensin converting enzyme inhibitor, aldosterone antagonist and loop diuretic are administered at doses that in combination result in a decrease in blood brain natriuretic peptide level in the subject as compared to the combination therapy of Claim 15.

41. The therapy of Claim 15 further characterized by administering said angiotensin converting enzyme inhibitor, aldosterone antagonist and loop diuretic in a sequential manner.

42. The therapy of Claim 15 further characterized by administering said angiotensin converting enzyme

inhibitor, aldosterone antagonist and loop diuretic in a substantially simultaneous manner.

43. The therapy of Claim 15 wherein said aldosterone antagonist is a spirolactone-type compound.

44. The therapy of Claim 15 wherein said spirolactone-type compound is spironolactone.

45. The therapy of Claim 15 wherein said angiotensin converting enzyme inhibitor is selected from the group consisting of alacepril, benazepril, captopril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, fosinoprilat, imidapril, lisinopril, perindopril, quinapril, ramipril, saralasin acetate, temocapril, trandolapril, ceranapril, moexipril, quinaprilat, spirapril, Bioproject BP1.137, Chiesi CHF 1514, Fisons FPL-66564, idrapril, Marion Merrell Dow MDL-100240, perindoprilat and Servier S-5590.

46. The therapy of Claim 15 wherein said angiotensin converting enzyme inhibitor is selected from the group consisting of alacepril, benazepril, captopril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, fosinoprilat, imidapril, lisinopril, perindopril, quinapril, ramipril, saralasin acetate, temocapril, trandolapril, ceranapril, moexipril, quinaprilat and spirapril.

47. The therapy of Claim 15 further characterized by said angiotensin converting enzyme inhibitor and said aldosterone antagonist being used in said combination therapy in a weight ratio range from about 0.1-to-one to about twenty-five-to-one of said angiotensin converting enzyme inhibitor to said aldosterone antagonist.

48. The therapy of Claim 15 wherein said weight ratio range is from about 0.5-to-one to about fifteen-to-one.

49. The therapy of Clàim 15 wherein said weight ratio range is from about 0.5-to-one to about five-to-one.

50. The therapy of Claim 15 wherein said angiotensin converting enzyme inhibitor is captopril, in a daily dose range from about 30 mg to about 80 mg per dose, or is enalapril in a dose range from about 5 mg to about 25 mg per dose.

51. The therapy of Claim 15 wherein said aldosterone antagonist is spironolactone in a daily dose range from about 1 mg to about 23 mg per dose.

52. The therapy of Claim 15 wherein said spironolactone daily dose is in a range from about 5 mg to about 20 mg.

53. The therapy of Claim 15 wherein said spironolactone daily dose is in a range from about 5 mg to about 15 mg.

54. The method of Claim 15 wherein the aldosterone antagonist is an epoxy-steroidal aldosterone antagonist.

55. The method of Claim 15 wherein the epoxy-containing compound has an epoxy moiety fused to the "C" ring of the steroidal nucleus of a 20-spiroxane compound.

56. The method of Claim 15 wherein the 20-spiroxane compound is characterized by the presence of a 9-alpha,11-beta-substituted epoxy moiety.

57. The method of Claim 15 wherein the epoxy-containing compound is selected from the group consisting of:

Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-,γ-lactone, methyl ester, (7α,11α,17α)-;

Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-dimethyl ester, (7α,11α,17α)-;

3'H-cyclopropa[6,7] pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, γ-lactone, (6β,7β,11β,17β)-;

Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo, 7-(1-methylethyl) ester, monopotassium salt, (7α,11α,17α)-;

Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, 7-methyl ester, monopotassium salt, (7α,11α,17α)-;

3'H-cyclopropa[6,7]pregna-1,4,6-triene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, γ-lactone, (6α,7α,11α)-;

3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, methyl ester, (6α,7α,11α,17α)-;

3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, monopotassium salt, (6α,7α,11α,17α)-;

3'H-cyclopropa[6,7]pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, γ-lactone, (6α,7α,11α,17α)-;

Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, γ-lactone, ethyl ester, (7α,11α,17α)-; and

Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, γ-lactone, 1-methylethyl ester, (7α, 11α, 17α)-.

58. The method of Claim 15 wherein the aldosterone antagonist is eplerenone.

59. The method of Claim 15 wherein the aldosterone antagonist is eplerenone in a daily dose range from about 0.5 mg to about 500 mg.

60. The method of Claim 15 wherein the aldosterone antagonist is an aldosterone antagonist other than spironolactone.

61. A composition comprising an angiotensin converting enzyme inhibitor, an aldosterone antagonist, a loop diuretic and digoxin, and the pharmaceutically acceptable salts, esters and prodrugs thereof.

62. A composition of Claim 63 comprising:

a first amount of an angiotensin converting enzyme inhibitor, or a pharmaceutically acceptable salt, ester or prodrug thereof;

a second amount of an aldosterone antagonist, or a pharmaceutically acceptable salt, ester or prodrug thereof;

a third amount of a loop diuretic, or a pharmaceutically acceptable salt, ester or prodrug thereof;

a fourth amount of digoxin, or a pharmaceutically acceptable salt, ester or prodrug thereof; and

a pharmaceutically acceptable carrier;

wherein the first, second, third and fourth amounts in combination comprise a therapeutically effective amount of said inhibitor, antagonist, loop diuretic and digoxin.

63. A composition of Claim 61 wherein the aldosterone antagonist is spironolactone.

64. A composition of Claim 61 wherein the aldosterone antagonist is eplerenone.

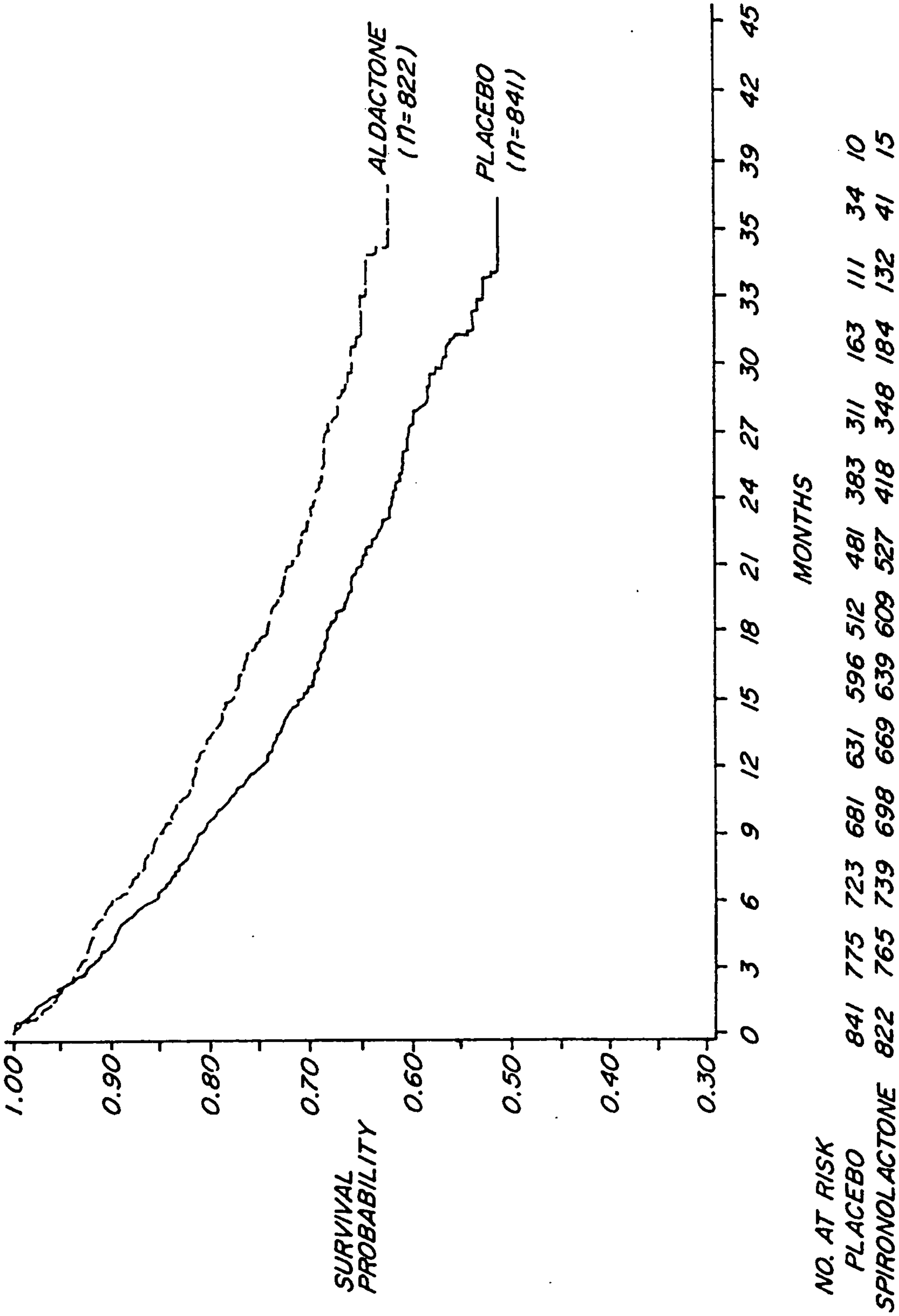

SURVIVAL PROBABILITY
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
ALDACTONE (n=822)
PLACEBO (n=841)
0 3 6 9 12 15 18 21 24 27 30 33 35 39 42 45
MONTHS
NO. AT RISK
PLACEBO 841 775 723 681 631 596 512 481 383 311 163 111 34 10
SPIRONOLACTONE 822 765 739 698 669 639 609 527 418 348 184 132 41 15

Fig. 1A

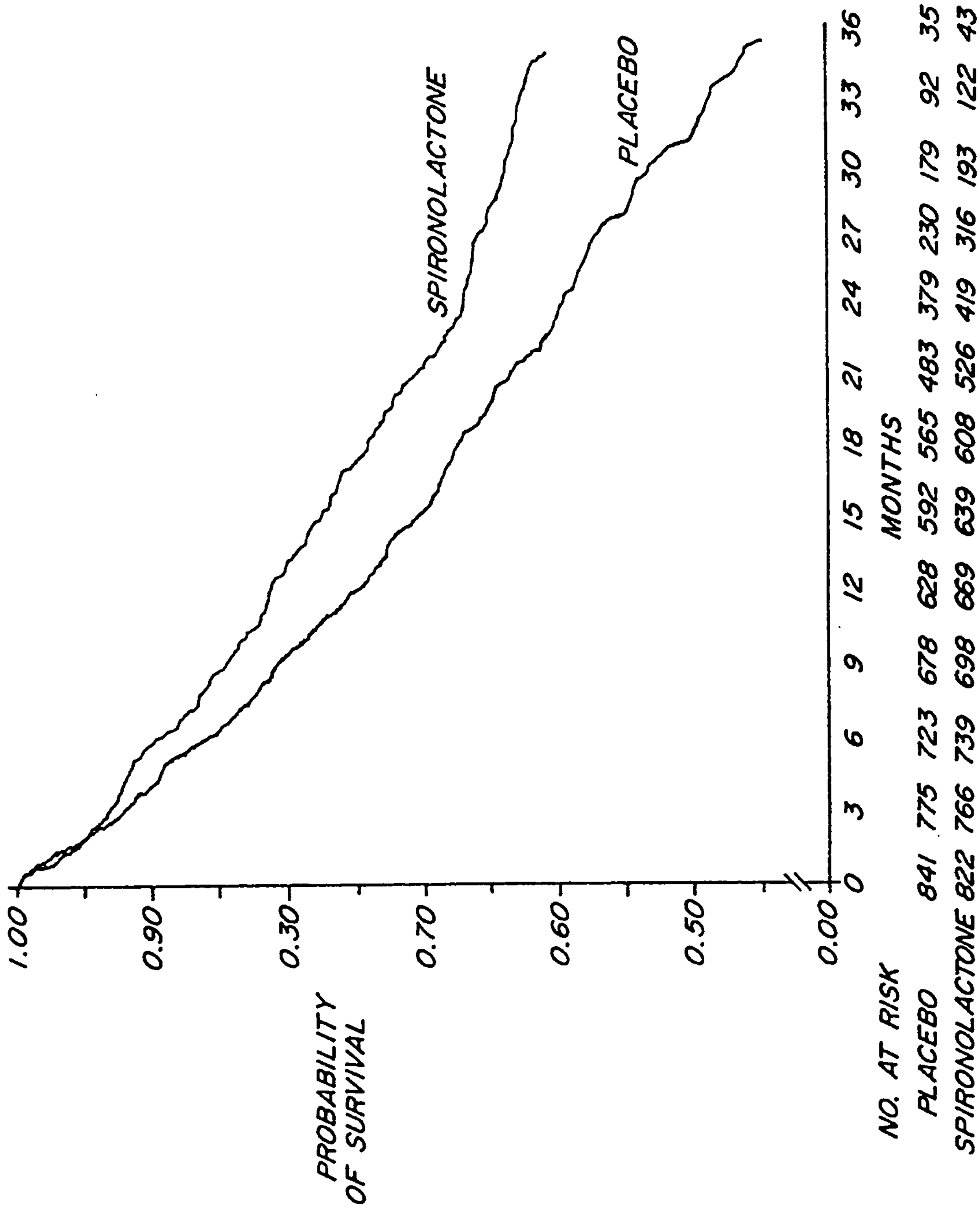

SPIRONOLACTONE
PLACEBO
PROBABILITY OF SURVIVAL
1.00
0.90
0.30
0.70
0.60
0.50
0.00
0
3
6
9
12
15
18
21
24
27
30
33
36
MONTHS
NO. AT RISK
PLACEBO 841 775 723 678 628 592 565 483 379 230 179 92 35
SPIRONOLACTONE 822 766 739 698 669 639 608 526 419 316 193 122 43

Fig. 1B

RISK REDUCTION FOR TOTAL MORTALITY
BY BASELINE GROUP

	RISK REDUCTION	95% CI FOR RISK REDUCTION
MEDIAN AGE (YEARS)		
≤67	0.23	(0.40, 0.01)
≥67	0.28	(0.41, 0.11)
LEFT VENTRICULAR EJECTION FRACTION (%)	0.18	(0.34, -0.01)
≤26	0.35	(0.49, 0.17)
≥ 26		
ETIOLOGY OF HEART FAILURE		
NON-ISCHEMIC	0.30	(0.45, 0.10)
ISCHEMIC	0.24	(0.38, 0.06)
CREATININE MEDIAN (μmol/L)		
≤106.0	0.37	(0.51, 0.18)
≥106.0	0.18	(0.33, -0.01)
DIGITALIS		
NO	0.13	(0.37, -0.18)
YES	0.31	(0.42, 0.17)
ACE INHIBITORS		
NO	0.04	(0.41, -0.56)
YES	0.28	(0.40, 0.15)
SEX		
FEMALE	0.26	(0.47, -0.02)
MALE	0.26	(0.39, 0.12)
POTASSIUM MEDIAN (mmol/L)		
≤4.2	0.27	(0.43, 0.06)
≥4.2	0.25	(0.40, 0.08)
NYHA		
CLASS III	0.25	(0.39, 0.08)
CLASS IV	0.24	(0.41, 0.01)0

Fig. 2

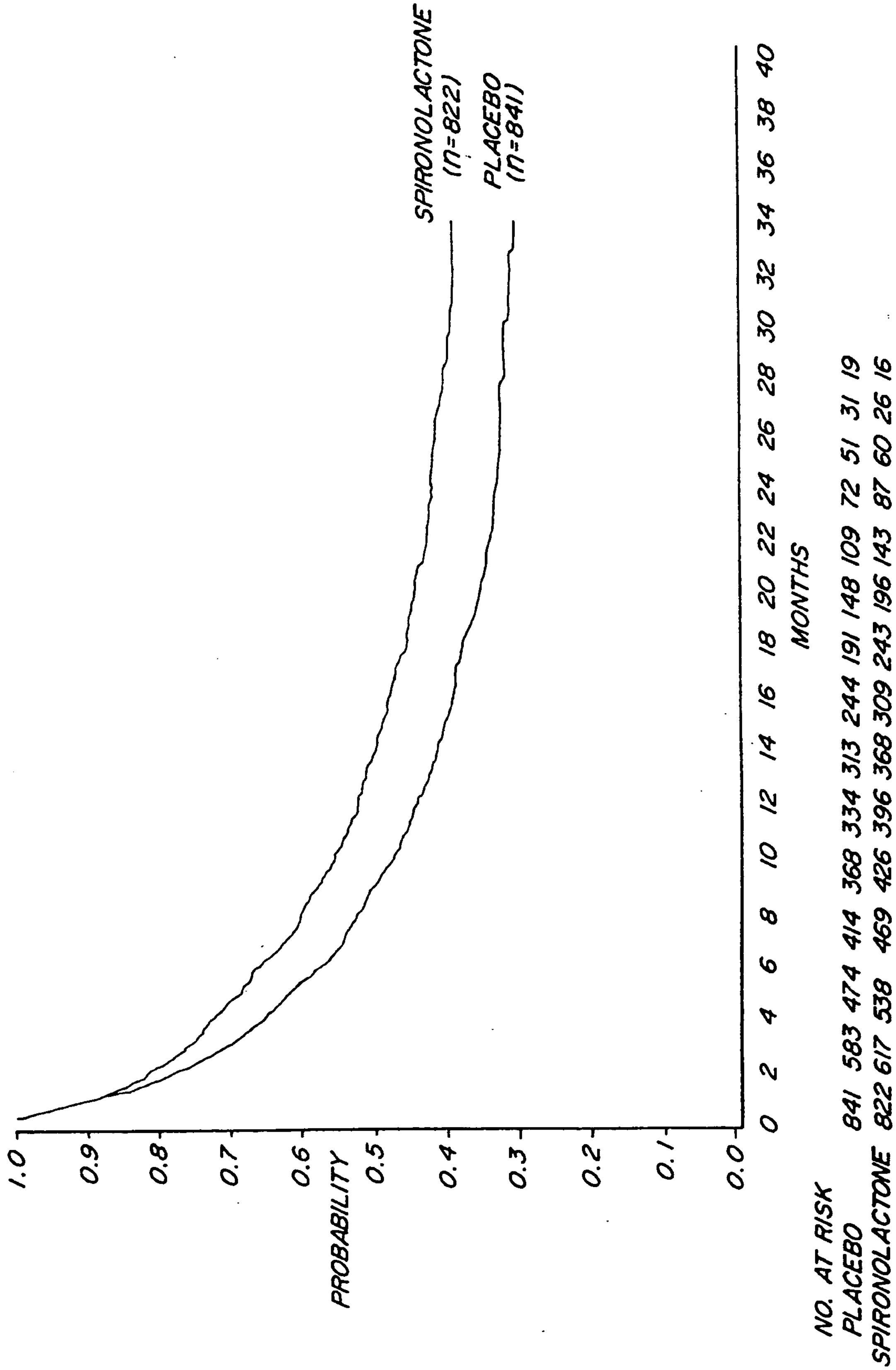

SPIRONOLACTONE
(n=822)
PLACEBO
(n=841)
PROBABILITY
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40
MONTHS
NO. AT RISK
PLACEBO 841 583 474 414 368 334 313 244 191 148 109 72 51 31 19
SPIRONOLACTONE 822 617 538 469 426 396 368 309 243 196 143 87 60 26 16

Fig. 3

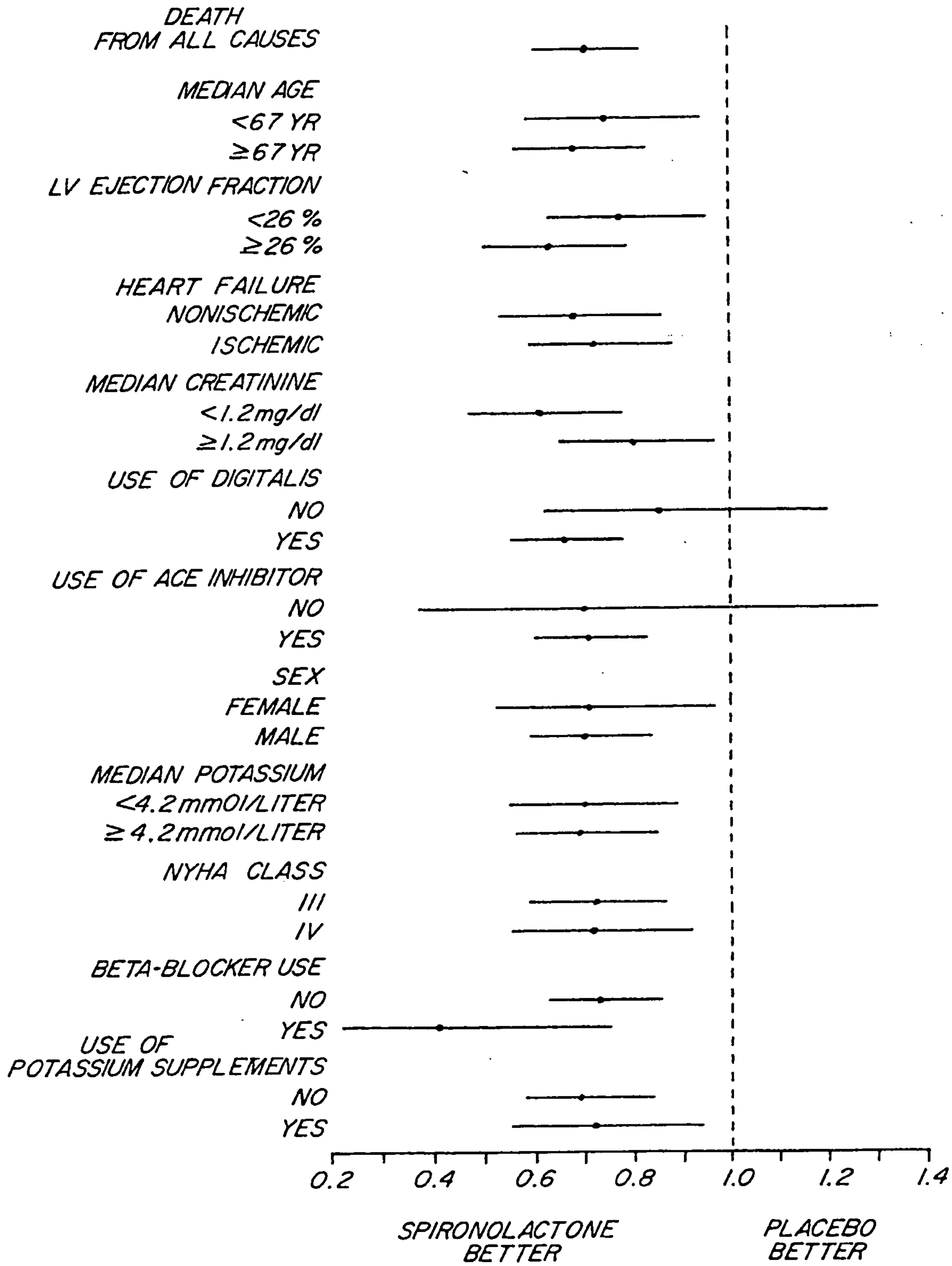

DEATH
FROM ALL CAUSES
MEDIAN AGE
<67 YR
≥67 YR
LV EJECTION FRACTION
<26 %
≥26 %
HEART FAILURE
NONISCHEMIC
ISCHEMIC
MEDIAN CREATININE
<1.2mg/dl
≥1.2mg/dl
USE OF DIGITALIS
NO
YES
USE OF ACE INHIBITOR
NO
YES
SEX
FEMALE
MALE
MEDIAN POTASSIUM
<4.2mmOl/LITER
≥4.2mmol/LITER
NYHA CLASS
III
IV
BETA-BLOCKER USE
NO
YES
USE OF
POTASSIUM SUPPLEMENTS
NO
YES
0.2
0.4
0.6
0.8
1.0
1.2
1.4
SPIRONOLACTONE
BETTER
PLACEBO
BETTER

Fig. 4

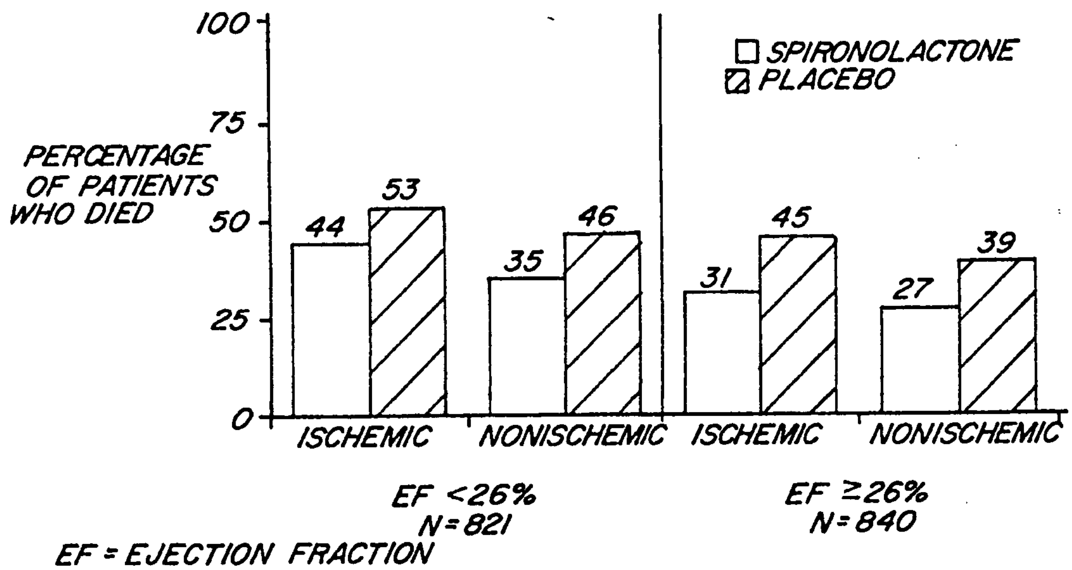

100
75
50
25
0
PERCENTAGE OF PATIENTS WHO DIED
SPIRONOLACTONE
PLACEBO
44
53
35
46
31
45
27
39
ISCHEMIC
NONISCHEMIC
ISCHEMIC
NONISCHEMIC
EF <26%
N=821
EF ≥26%
N=840
EF = EJECTION FRACTION

Fig. 5

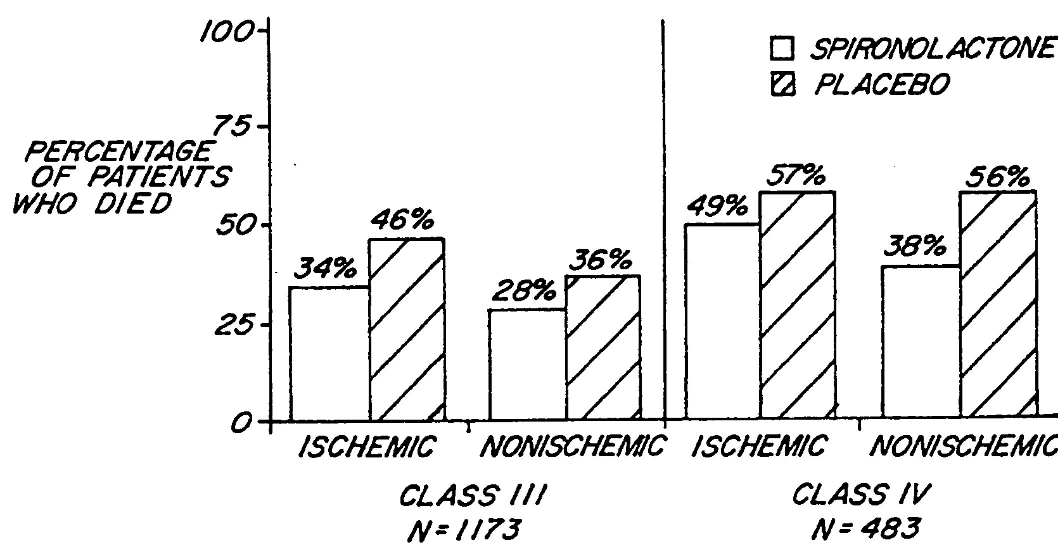

100
75
50
25
0
PERCENTAGE OF PATIENTS WHO DIED
SPIRONOLACTONE
PLACEBO
34%
46%
28%
36%
49%
57%
38%
56%
ISCHEMIC
NONISCHEMIC
ISCHEMIC
NONISCHEMIC
CLASS III
N=1173
CLASS IV
N=483

Fig. 6

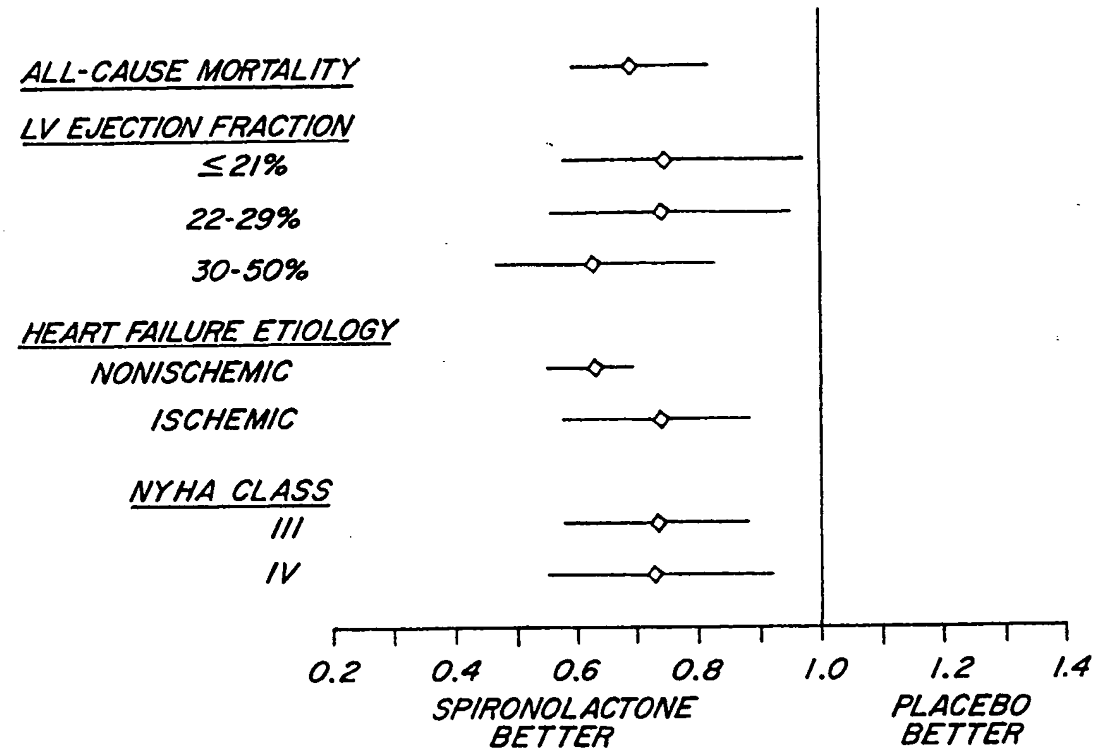

ALL-CAUSE MORTALITY
LV EJECTION FRACTION
≤21%
22-29%
30-50%
HEART FAILURE ETIOLOGY
NONISCHEMIC
ISCHEMIC
NYHA CLASS
III
IV
0.2
0.4
0.6
0.8
1.0
1.2
1.4
SPIRONOLACTONE BETTER
PLACEBO BETTER

Fig. 7

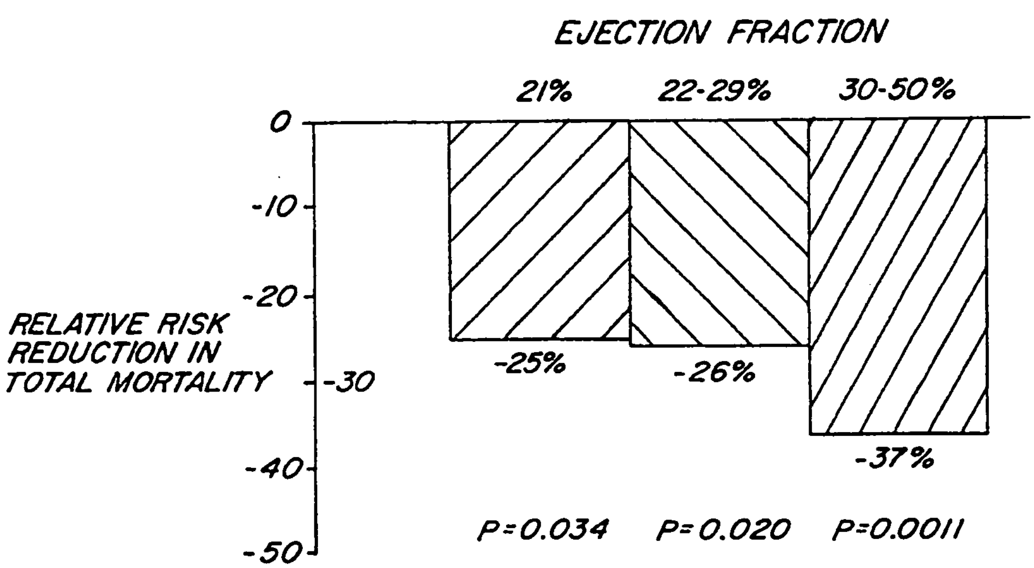

EJECTION FRACTION
21%
22-29%
30-50%
0
-10
-20
-30
-40
-50
RELATIVE RISK REDUCTION IN TOTAL MORTALITY
-25%
-26%
-37%
P=0.034
P=0.020
P=0.0011

Fig. 8

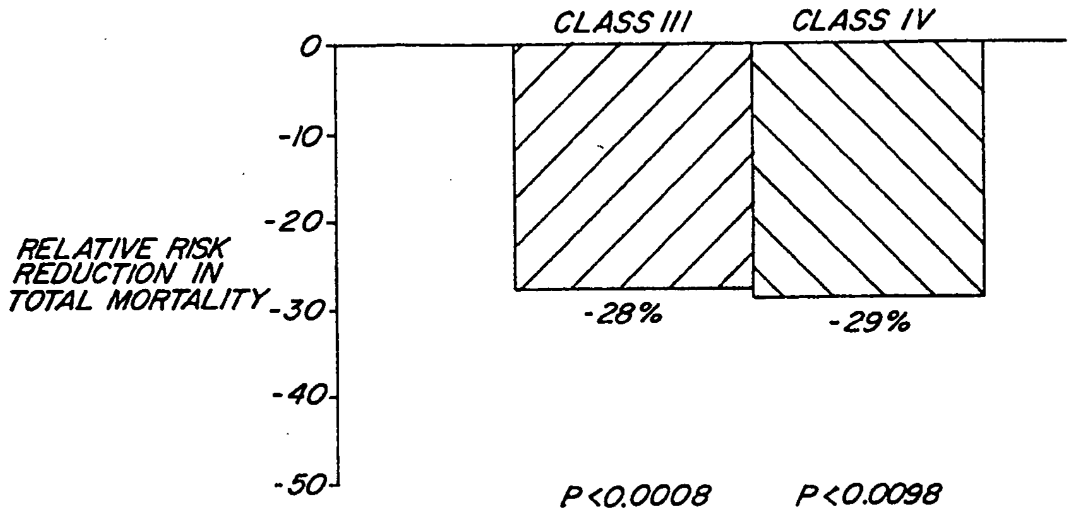

CLASS III
CLASS IV
0
-10
-20
-30
-40
-50
RELATIVE RISK REDUCTION IN TOTAL MORTALITY
-28%
-29%
P<0.0008
P<0.0098

Fig. 9

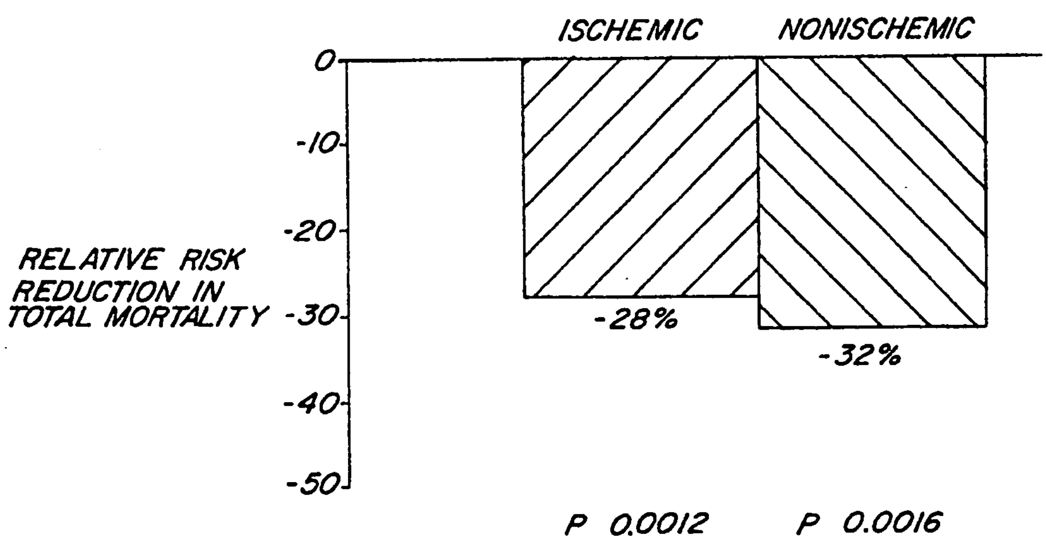

ISCHEMIC
NONISCHEMIC
0
-10
-20
-30
-40
-50
RELATIVE RISK REDUCTION IN TOTAL MORTALITY
-28%
-32%
P 0.0012
P 0.0016

Fig. 10

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 45/06, 38/55, A61P 9/00 — A3

(11) International Publication Number: WO 00/27380

(43) International Publication Date: 18 May 2000 (18.05.00)

(21) International Application Number: PCT/US99/26206

(22) International Filing Date: 5 November 1999 (05.11.99)

(30) Priority Data:

60/107,398	6 November 1998 (06.11.98)	US
60/122,977	5 March 1999 (05.03.99)	US
60/122,978	5 March 1999 (05.03.99)	US

(71) Applicant *(for all designated States except US)*: G.D. SEARLE & CO. [US/US]; Corporate Patent Department, P.O. Box 5110, Chicago, IL 60680-5110 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: PEREZ, Alfonso, T. [US/US]; 1286 Cascade Court, Lake Forest, IL 60045 (US). LACHAPELLE, Richard, J. [US/US]; 1618 Central Avenue, Wilmette, IL 60091 (US). RONIKER, Barbara [US/US]; 1530 Dearborn Parkway, Chicago, IL 60610 (US). ASNER, Debra, J. [US/US]; 9009 Marmora Avenue, Morton Grove, IL 60053 (US). ALEXANDER, John, C. [US/US]; 1100 Pelham Road, Winnetka, IL 60093 (US).

(74) Agents: KEANE, J., Timothy et al.; G.D. Searle & Co., Corporate Patent Department, P.O. Box 5110, Chicago, IL 60680-5110 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(88) Date of publication of the international search report: 24 August 2000 (24.08.00)

(54) Title: COMBINATION THERAPY OF ANGIOTENSIN CONVERTING ENZYME INHIBITOR AND ALDOSTERONE ANTAGONIST FOR REDUCING MORBIDITY AND MORTALITY FROM CARDIOVASCULAR DISEASE

(57) Abstract

Combinations of an ACE inhibitor, an aldosterone antagonist, and a loop diuretic are described for use in treatment of circulatory disorders. Of particular interest are therapies using captopril, enalapril or lisinopril co-administered with spironolactone. This co-therapy would be particularly useful to reduce the death rate or the number of non-fatal hospitalizations or prevent the progression of congestive heart failure in patients with cardiovascular disease.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

Inte   nal Application No
PCT/US 99/26206

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61K38/55 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 24373 A (G.D. SEARLE) 15 August 1996 (1996-08-15) claims 1-11,13,14,22-25 page 4, line 26-33 page 8, line 31-37 page 17, line 17-22 page 18, line 7-9 page 22 page 27, line 19-21 ---	1-27,32, 33,37, 39, 43-56, 62-65

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 April 2000	16/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Peeters, J

1

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/US 99/26206

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 24372 A (G.D. SEARLE) 15 August 1996 (1996-08-15) claims 1-14,22,23 page 4, line 29-36 page 19, line 1-3 page 23 ---	1-27,32, 33, 37-39, 43-56, 62-65
X	WO 96 40255 A (G.D. SEARLE) 19 December 1996 (1996-12-19) claims 1-5,13-16 page 6, line 17-20 page 23, line 29 -page 24, line 1 ---	1-4, 8-10, 15-23, 32,33, 37, 43-45, 56-59
X	WO 96 40256 A (G.D. SEARLE) 19 December 1996 (1996-12-19) claims 1,11-13,16-18 page 14, line 33-38 ---	1-5, 8-10, 15-23, 32,33, 37, 43-46, 56-59
X	T.KINUGAWA E.A.: "Effects of spironolactone on exercise capacity and neurohormonal factors in patients with heart failure treated with loop diuretics and angiotensin-converting enzyme inhibitor" GENERAL PHARMACOLOGY, vol. 31, no. 1, 1998, page 93-99 XP002136087 page 93 page 94, column 1 page 95 page 96, column 2 page 97, column 1 page 98, column 1 -----	1-7, 15-23, 32-48, 53-55

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/26206

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9624373 A	15-08-1996	AU 5354196 A	27-08-1996
		BR 9604882 A	19-05-1998
		CA 2212713 A	15-08-1996
		EP 0808172 A	26-11-1997
		JP 11507012 T	22-06-1999
WO 9624372 A	15-08-1996	AU 4866196 A	27-08-1996
		BR 9607612 A	09-06-1998
		CA 2212712 A	15-08-1996
		EP 0808171 A	26-11-1997
		JP 10513472 T	22-12-1998
WO 9640255 A	19-12-1996	AU 6039296 A	30-12-1996
WO 9640256 A	19-12-1996	AU 5982296 A	30-12-1996